US009192715B2

(12) **United States Patent**
Gelfand et al.

(10) **Patent No.: US 9,192,715 B2**
(45) **Date of Patent: *Nov. 24, 2015**

(54) **METHODS FOR RENAL NERVE BLOCKING**

(71) Applicant: **Medtronic Ardian Luxembourg S.a.r.l.**, Luxembourg (LU)

(72) Inventors: **Mark Gelfand**, New York, NY (US); **Howard R. Levin**, Teaneck, NJ (US)

(73) Assignee: **Medtronic Ardian Luxembourg S.a.r.l.**, Luxembourg (LU)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/221,536**

(22) Filed: **Mar. 21, 2014**

(65) **Prior Publication Data**

US 2014/0324016 A1 Oct. 30, 2014

Related U.S. Application Data

(63) Continuation of application No. 11/133,925, filed on May 20, 2005, now Pat. No. 8,771,252, which is a continuation of application No. 10/900,199, filed on Jul. 28, 2004, now Pat. No. 6,978,174, which is a continuation-in-part of application No. 10/408,665, filed on Apr. 8, 2003, now Pat. No. 7,162,303.

(60) Provisional application No. 60/370,190, filed on Apr. 8, 2002, provisional application No. 60/415,575, filed on Oct. 3, 2002, provisional application No. 60/442,970, filed on Jan. 29, 2003.

(51) **Int. Cl.**

A61M 5/145	(2006.01)
A61M 5/142	(2006.01)
A61M 5/172	(2006.01)

(Continued)

(52) **U.S. Cl.**

CPC ***A61M 5/145*** (2013.01); ***A61K 9/0012*** (2013.01); ***A61K 9/7007*** (2013.01); ***A61L 29/146*** (2013.01); ***A61M 5/14276*** (2013.01); ***A61M 5/1723*** (2013.01); ***A61N 1/326*** (2013.01); ***A61N 1/36114*** (2013.01); *A61M 2005/14513* (2013.01); *A61M 2210/1082* (2013.01); *A61N 1/0551* (2013.01); *A61N 1/36007* (2013.01);

(Continued)

(58) **Field of Classification Search**

CPC A61M 5/14276; A61M 5/1723; A61M 5/145; A61M 2005/14513; A61N 1/326; A61N 1/36007; A61N 1/36117; A61N 1/3627; A61K 9/0012; A61K 9/7007; A61L 29/146

USPC 604/890.1, 891.1, 131, 151, 522; 607/3

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,130,758	A	9/1938	Rose
2,276,995	A	3/1942	Milinowski

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2575458	3/2006
DE	3151180	8/1982

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 60/813,589, filed Dec. 29, 2005, Demarais et al.

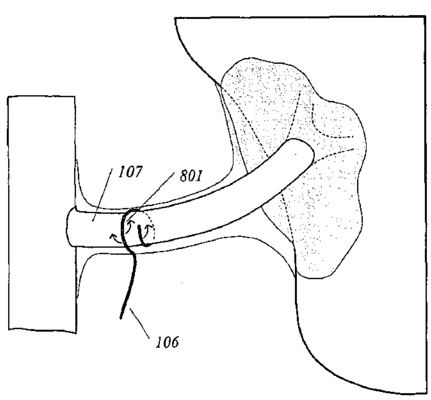
(Continued)

Primary Examiner — Mark W Bockelman

(57) **ABSTRACT**

A method and apparatus for treatment of cardiac and renal diseases associated with the elevated sympathetic renal nerve activity by implanting a device to block the renal nerve signals to and from the kidney. The device can be a drug pump or a drug eluding implant for targeted delivery of a nerve-blocking agent to the periarterial space of the renal artery.

23 Claims, 9 Drawing Sheets



(51) **Int. Cl.**

A61N 1/32	(2006.01)
A61K 9/00	(2006.01)
A61K 9/70	(2006.01)
A61L 29/14	(2006.01)
A61N 1/05	(2006.01)
A61N 1/36	(2006.01)
A61N 1/362	(2006.01)

(52) **U.S. Cl.**
CPC *A61N 1/3627* (2013.01); *A61N 1/36117* (2013.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,276,996	A	3/1942	Milinowski
3,043,310	A	7/1962	Milinowski
3,127,895	A	4/1964	Kendall et al.
3,181,535	A	5/1965	Milinowski
3,270,746	A	9/1966	Kendall et al.
3,329,149	A	7/1967	Kendall et al.
3,522,811	A	8/1970	Schwartz et al.
3,563,246	A	2/1971	Puharich et al.
3,650,277	A	3/1972	Sjostrand et al.
3,670,737	A	6/1972	Pearo
3,752,162	A	8/1973	Newash
3,760,812	A	9/1973	Timm et al.
3,774,620	A	11/1973	Hansjurgens et al.
3,794,022	A	2/1974	Nawracaj et al.
3,800,802	A	4/1974	Berry et al.
3,803,463	A	4/1974	Cover
3,894,532	A	7/1975	Morey
3,895,639	A	7/1975	Rodler et al.
3,897,789	A	8/1975	Blanchard
3,911,930	A	10/1975	Hagfors et al.
3,952,751	A	4/1976	Yarger
3,987,790	A	10/1976	Eckenhoff et al.
4,011,861	A	3/1977	Enger
4,026,300	A	5/1977	DeLuca et al.
4,055,190	A	10/1977	Tany et al.
4,071,033	A	1/1978	Nawracaj et al.
4,105,017	A	8/1978	Ryaby et al.
4,141,365	A	2/1979	Fischell et al.
4,266,532	A	5/1981	Ryaby et al.
4,266,533	A	5/1981	Ryaby et al.
4,305,115	A	12/1981	Armitage et al.
4,315,503	A	2/1982	Ryaby et al.
4,360,019	A	11/1982	Portner et al.
4,379,462	A	4/1983	Borkan et al.
4,405,305	A	9/1983	Stephen et al.
4,454,883	A	6/1984	Fellus et al.
4,467,808	A	8/1984	Brighton et al.
4,487,603	A	12/1984	Harris
4,530,840	A	7/1985	Tice et al.
4,587,975	A	5/1986	Salo et al.
4,602,624	A	7/1986	Naples et al.
4,608,985	A	9/1986	Crish et al.
4,649,936	A	3/1987	Ungar et al.
4,671,286	A	6/1987	Renault et al.
4,674,482	A	6/1987	Waltonen et al.
4,692,147	A	9/1987	Duggan
4,715,852	A	12/1987	Reinicke et al.
4,774,967	A	10/1988	Zanakis et al.
4,791,931	A	12/1988	Slate
4,816,016	A	3/1989	Schulte et al.
4,824,436	A	4/1989	Wolinsky
4,852,573	A	8/1989	Kennedy
4,865,845	A	9/1989	Eckenhoff et al.
4,976,711	A	12/1990	Parins et al.
4,979,511	A	12/1990	Terry, Jr.
4,981,146	A	1/1991	Bertolucci
4,998,532	A	3/1991	Griffith
5,006,119	A	4/1991	Acker et al.
5,014,699	A	5/1991	Pollack et al.
5,019,034	A	5/1991	Weaver et al.
5,057,318	A	10/1991	Magruder et al.
5,058,584	A	10/1991	Bourgeois et al.
5,059,423	A	10/1991	Magruder et al.
5,061,492	A	10/1991	Okada et al.
5,087,244	A	2/1992	Wolinsky et al.
5,094,242	A	3/1992	Gleason et al.
5,111,815	A	5/1992	Mower
5,112,614	A	5/1992	Magruder et al.
5,125,928	A	6/1992	Parins et al.
5,131,409	A	7/1992	Lobarev et al.
5,137,727	A	8/1992	Eckenhoff
5,188,837	A	2/1993	Domb
5,193,048	A	3/1993	Kaufman et al.
5,193,539	A	3/1993	Schulman et al.
5,193,540	A	3/1993	Schulman et al.
5,199,428	A	4/1993	Obel et al.
5,203,326	A	4/1993	Collins et al.
5,213,098	A	5/1993	Bennett et al.
5,215,086	A	6/1993	Terry, Jr. et al.
5,231,988	A	8/1993	Wernicke et al.
5,234,692	A	8/1993	Magruder et al.
5,234,693	A	8/1993	Magruder et al.
5,251,634	A	10/1993	Weinberg
5,251,643	A	10/1993	Osypka et al.
5,263,480	A	11/1993	Wernicke et al.
5,269,303	A	12/1993	Wernicke et al.
5,282,468	A	2/1994	Klepinski
5,282,785	A	2/1994	Shapland et al.
5,286,254	A	2/1994	Shapland et al.
5,299,569	A	4/1994	Wernicke et al.
5,300,068	A	4/1994	Rosar et al.
5,304,120	A	4/1994	Crandell et al.
5,304,206	A	4/1994	Baker, Jr. et al.
5,317,155	A	5/1994	King
5,324,255	A	6/1994	Passafaro et al.
5,324,316	A	6/1994	Schulman et al.
5,334,193	A	8/1994	Nardella
5,335,657	A	8/1994	Terry, Jr. et al.
5,338,662	A	8/1994	Sadri
5,351,394	A	10/1994	Weinberg
5,358,514	A	10/1994	Schulman et al.
5,368,591	A	11/1994	Lennox et al.
5,370,680	A	12/1994	Proctor
5,389,069	A	2/1995	Weaver
5,397,308	A	3/1995	Ellis et al.
5,397,338	A	3/1995	Grey et al.
5,400,784	A	3/1995	Durand et al.
5,405,367	A	4/1995	Schulman et al.
5,419,777	A	5/1995	Hofling
5,423,744	A	6/1995	Gencheff et al.
5,429,634	A	7/1995	Narciso, Jr.
5,433,739	A	7/1995	Sluijter et al.
5,439,440	A	8/1995	Hofmann
5,454,782	A	10/1995	Perkins
5,454,809	A	10/1995	Janssen
5,458,568	A	10/1995	Racchini et al.
5,458,626	A	10/1995	Krause
5,458,631	A	10/1995	Xavier
5,464,395	A	11/1995	Faxon et al.
5,470,352	A	11/1995	Rappaport
5,472,406	A	12/1995	de la Torre et al.
5,478,303	A	12/1995	Foley-Nolan et al.
5,484,400	A	1/1996	Edwards et al.
5,494,822	A	2/1996	Sadri
5,498,238	A	3/1996	Shapland et al.
5,499,971	A	3/1996	Shapland et al.
5,505,700	A	4/1996	Leone et al.
5,507,724	A	4/1996	Hofmann et al.
5,507,791	A	4/1996	Sit'ko et al.
5,531,778	A	7/1996	Maschino et al.
5,538,504	A	7/1996	Linden et al.
5,540,730	A	7/1996	Terry, Jr. et al.
5,540,734	A	7/1996	Zabara
5,553,611	A	9/1996	Budd et al.
5,560,360	A	10/1996	Filler et al.
5,569,198	A	10/1996	Racchini
5,571,147	A	11/1996	Sluijter et al.
5,571,150	A	11/1996	Wernicke et al.
5,573,552	A	11/1996	Hansjurgens et al.

(56) References Cited

U.S. PATENT DOCUMENTS

5,584,863 A 12/1996 Rauch et al.
5,588,964 A 12/1996 Imran et al.
5,589,192 A 12/1996 Okabe et al.
5,599,345 A 2/1997 Edwards et al.
5,618,563 A 4/1997 Berde et al.
5,626,576 A 5/1997 Janssen
5,626,862 A 5/1997 Brem et al.
5,628,730 A 5/1997 Shapland et al.
5,634,462 A 6/1997 Tyler et al.
5,634,899 A 6/1997 Shapland et al.
5,672,174 A 9/1997 Gough et al.
5,688,266 A 11/1997 Edwards et al.
5,689,877 A 11/1997 Grill, Jr. et al.
5,690,691 A 11/1997 Chen et al.
5,700,282 A 12/1997 Zabara
5,700,485 A 12/1997 Berde et al.
5,704,908 A 1/1998 Hofmann et al.
5,707,400 A 1/1998 Terry, Jr. et al.
5,709,874 A 1/1998 Hanson et al.
5,711,326 A 1/1998 Thies et al.
5,713,847 A 2/1998 Howard, III et al.
5,722,401 A 3/1998 Pietroski et al.
5,723,001 A 3/1998 Pilla et al.
5,725,563 A 3/1998 Klotz et al.
5,728,396 A 3/1998 Peery et al.
5,747,060 A 5/1998 Sackler et al.
5,755,750 A 5/1998 Petruska et al.
5,756,115 A 5/1998 Moo-Young et al.
5,772,590 A 6/1998 Webster, Jr.
5,792,187 A 8/1998 Adams
5,800,464 A 9/1998 Kieval
5,807,306 A 9/1998 Shapland et al.
5,810,802 A 9/1998 Panescu et al.
5,814,079 A 9/1998 Kieval
5,824,087 A 10/1998 Aspden et al.
5,836,935 A 11/1998 Ashton et al.
RE35,987 E 12/1998 Harris et al.
5,843,069 A 12/1998 Butler et al.
5,861,021 A 1/1999 Thome et al.
5,865,787 A 2/1999 Shapland et al.
5,871,449 A 2/1999 Brown
5,891,181 A 4/1999 Zhu
5,893,885 A 4/1999 Webster et al.
5,906,636 A 5/1999 Casscells, III et al.
5,906,817 A 5/1999 Moullier et al.
5,913,876 A 6/1999 Taylor et al.
5,916,154 A 6/1999 Hobbs et al.
5,916,239 A 6/1999 Geddes et al.
5,919,187 A 7/1999 Guglielmi et al.
5,922,340 A 7/1999 Berde et al.
5,924,997 A 7/1999 Campbell
5,928,272 A 7/1999 Adkins et al.
5,935,075 A 8/1999 Casscells et al.
5,944,710 A 8/1999 Dev et al.
5,954,719 A 9/1999 Chen et al.
5,983,131 A 11/1999 Weaver et al.
5,983,141 A 11/1999 Sluijter et al.
6,006,134 A 12/1999 Hill et al.
6,009,877 A 1/2000 Edwards
6,010,613 A 1/2000 Walters et al.
6,026,326 A 2/2000 Bardy
6,041,252 A 3/2000 Walker et al.
6,051,017 A 4/2000 Loeb et al.
6,058,328 A 5/2000 Levine et al.
6,058,331 A 5/2000 King
6,066,134 A 5/2000 Eggers et al.
6,073,048 A 6/2000 Kieval et al.
6,077,227 A 6/2000 Miesel et al.
6,086,527 A 7/2000 Talpade
6,117,101 A 9/2000 Diederich et al.
6,122,548 A 9/2000 Starkebaum et al.
6,123,718 A 9/2000 Tu et al.
6,135,999 A 10/2000 Fanton et al.
6,146,380 A 11/2000 Racz et al.
6,161,048 A 12/2000 Sluijter et al.
6,171,306 B1 1/2001 Swanson et al.
6,178,349 B1 1/2001 Kieval
6,190,353 B1 2/2001 Makower et al.
6,192,889 B1 2/2001 Morrish
6,205,361 B1 3/2001 Kuzma et al.
6,208,894 B1 3/2001 Schulman et al.
6,214,032 B1 4/2001 Loeb et al.
6,219,577 B1 4/2001 Brown, III et al.
6,224,592 B1 5/2001 Eggers et al.
6,238,702 B1 5/2001 Berde et al.
6,245,026 B1 6/2001 Campbell et al.
6,246,912 B1 6/2001 Sluijter et al.
6,251,130 B1 6/2001 Dobak, III et al.
6,254,598 B1 7/2001 Edwards et al.
6,258,087 B1 7/2001 Edwards et al.
6,259,952 B1 7/2001 Sluijter et al.
6,269,269 B1 7/2001 Ottenhoff et al.
6,272,377 B1 8/2001 Sweeney et al.
6,272,383 B1 8/2001 Grey et al.
6,273,886 B1 8/2001 Edwards et al.
6,280,377 B1 8/2001 Talpade
6,283,951 B1 9/2001 Flaherty et al.
6,287,304 B1 9/2001 Eggers et al.
6,287,608 B1 9/2001 Levin et al.
6,292,695 B1 9/2001 Webster, Jr. et al.
6,304,777 B1 10/2001 Ben-Haim et al.
6,304,787 B1 10/2001 Kuzma et al.
6,306,423 B1 10/2001 Donovan et al.
6,314,325 B1 11/2001 Fitz
6,322,558 B1 11/2001 Taylor et al.
6,322,559 B1 11/2001 Daulton et al.
6,326,020 B1 12/2001 Kohane et al.
6,326,177 B1 12/2001 Schoenbach et al.
6,328,699 B1 12/2001 Eigler et al.
6,334,069 B1 12/2001 George et al.
6,347,247 B1 2/2002 Dev et al.
6,353,763 B1 3/2002 George et al.
6,356,786 B1 3/2002 Rezai et al.
6,356,787 B1 3/2002 Rezai et al.
6,366,808 B1 4/2002 Schroeppel et al.
6,366,815 B1 4/2002 Haugland et al.
6,393,324 B2 5/2002 Gruzdowich et al.
6,400,982 B2 6/2002 Sweeney et al.
6,405,079 B1 6/2002 Ansarinia
6,405,732 B1 6/2002 Edwards et al.
6,413,255 B1 7/2002 Stern
6,415,183 B1 7/2002 Scheiner et al.
6,415,187 B1 7/2002 Kuzma et al.
6,438,423 B1 8/2002 Rezai et al.
6,442,424 B1 8/2002 Ben-Haim et al.
6,449,507 B1 9/2002 Hill et al.
6,450,942 B1 9/2002 Lapanashvili et al.
6,461,314 B1 10/2002 Pant et al.
6,464,687 B1 10/2002 Ishikawa et al.
6,473,644 B1 10/2002 Terry, Jr. et al.
6,482,619 B1 11/2002 Rubinsky et al.
6,488,679 B1 12/2002 Swanson et al.
6,506,189 B1 1/2003 Rittman, III et al.
6,508,774 B1 1/2003 Acker et al.
6,514,226 B1 2/2003 Levin et al.
6,516,211 B1 2/2003 Acker et al.
6,517,811 B2 2/2003 John et al.
6,522,926 B1 2/2003 Kieval et al.
6,522,932 B1 2/2003 Kuzma et al.
6,524,607 B1 2/2003 Goldenheim et al.
6,534,081 B2 3/2003 Goldenheim et al.
6,536,949 B1 3/2003 Heuser
6,542,781 B1 4/2003 Koblish et al.
6,564,096 B2 5/2003 Mest
6,571,127 B1 5/2003 Ben-Haim et al.
6,592,567 B1 7/2003 Levin et al.
6,599,256 B1 7/2003 Acker et al.
6,600,954 B2 7/2003 Cohen et al.
6,600,956 B2 7/2003 Maschino et al.
6,601,459 B1 8/2003 Jenni
6,605,084 B2 8/2003 Acker et al.
6,613,045 B1 9/2003 Laufer et al.
6,615,071 B1 9/2003 Casscells, III et al.
6,616,624 B1 9/2003 Kieval

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,620,151	B2	9/2003	Blischak et al.
6,622,041	B2	9/2003	Terry, Jr. et al.
6,622,731	B2	9/2003	Daniel et al.
6,635,054	B2	10/2003	Fjield et al.
6,654,636	B1	11/2003	Dev et al.
6,666,845	B2	12/2003	Hooper et al.
6,669,655	B1	12/2003	Acker et al.
6,671,556	B2	12/2003	Osorio et al.
6,672,312	B2	1/2004	Acker
6,676,657	B2	1/2004	Wood
6,681,136	B2	1/2004	Schuler et al.
6,684,105	B2	1/2004	Cohen et al.
6,690,971	B2	2/2004	Schauerte et al.
6,692,738	B2	2/2004	MacLaughlin et al.
6,697,670	B2	2/2004	Chomenky et al.
6,711,444	B2	3/2004	Koblish
6,718,208	B2	4/2004	Hill et al.
6,735,471	B2	5/2004	Hill et al.
6,738,663	B2	5/2004	Schroeppel et al.
6,749,598	B1	6/2004	Keren et al.
6,767,544	B2	7/2004	Brooks et al.
6,786,904	B2	9/2004	Doscher et al.
6,795,728	B2	9/2004	Chornenky et al.
6,845,267	B2	1/2005	Harrison et al.
6,850,801	B2	2/2005	Kieval et al.
6,862,479	B1	3/2005	Whitehurst et al.
6,865,416	B2	3/2005	Dev et al.
6,885,888	B2	4/2005	Rezai
6,893,414	B2	5/2005	Goble et al.
6,916,656	B2	7/2005	Walters et al.
6,927,049	B2	8/2005	Rubinsky et al.
6,936,047	B2	8/2005	Nasab et al.
6,939,345	B2	9/2005	KenKnight et al.
6,939,346	B2	9/2005	Kannenberg et al.
6,958,060	B2	10/2005	Mathiesen et al.
6,969,388	B2	11/2005	Goldman et al.
6,972,013	B1	12/2005	Zhang et al.
6,978,174	B2	12/2005	Gelfand et al.
6,985,774	B2	1/2006	Kieval et al.
6,994,700	B2	2/2006	Elkins et al.
6,994,706	B2	2/2006	Chornenky et al.
7,004,911	B1	2/2006	Tu et al.
7,054,685	B2	5/2006	Dimmer et al.
7,063,679	B2	6/2006	Maguire et al.
7,081,114	B2	7/2006	Rashidi
7,081,115	B2	7/2006	Taimisto
7,083,614	B2	8/2006	Fjield et al.
7,122,019	B1	10/2006	Kesten et al.
7,127,284	B2	10/2006	Seward
7,141,041	B2	11/2006	Seward
7,155,284	B1	12/2006	Whitehurst et al.
7,162,303	B2	1/2007	Levin et al.
7,191,015	B2	3/2007	Lamson et al.
7,273,469	B1	9/2007	Chan et al.
7,373,204	B2	5/2008	Gelfand et al.
7,444,183	B2	10/2008	Knudson et al.
7,465,298	B2	12/2008	Seward et al.
7,617,005	B2	11/2009	Demarais et al.
7,620,451	B2	11/2009	Demarais et al.
7,647,115	B2	1/2010	Levin et al.
7,653,438	B2	1/2010	Deem et al.
7,666,163	B2	2/2010	Seward et al.
7,691,080	B2	4/2010	Seward et al.
7,717,948	B2	5/2010	Demarais et al.
7,744,584	B2	6/2010	Seward et al.
7,756,583	B2	7/2010	Demarais et al.
7,917,208	B2	3/2011	Yomtov et al.
8,016,786	B2	9/2011	Seward et al.
8,027,740	B2	9/2011	Altman et al.
8,131,371	B2	3/2012	Demarais et al.
8,145,317	B2	3/2012	Demarais et al.
8,150,519	B2	4/2012	Demarais et al.
8,150,520	B2	4/2012	Demarais et al.
8,175,711	B2	5/2012	Demarais et al.
8,399,443	B2	3/2013	Seward
8,465,752	B2	6/2013	Seward
8,562,573	B1	10/2013	Fischell
8,663,190	B2	3/2014	Fischell et al.
8,708,995	B2	4/2014	Seward et al.
8,721,590	B2	5/2014	Seward et al.
8,740,849	B1	6/2014	Fischell et al.
8,975,233	B2	3/2015	Stein et al.
2001/0044596	A1	11/2001	Jaafar
2002/0002329	A1	1/2002	Avitall
2002/0026222	A1	2/2002	Schauerte et al.
2002/0026228	A1	2/2002	Schauerte
2002/0032468	A1	3/2002	Hill et al.
2002/0038137	A1	3/2002	Stein
2002/0040204	A1	4/2002	Dev et al.
2002/0045853	A1	4/2002	Dev et al.
2002/0065541	A1	5/2002	Fredricks et al.
2002/0072782	A1	6/2002	Osorio et al.
2002/0107553	A1	8/2002	Hill et al.
2002/0116030	A1	8/2002	Rezai
2002/0120304	A1	8/2002	Mest
2002/0165532	A1	11/2002	Hill et al.
2002/0165586	A1	11/2002	Hill et al.
2002/0169413	A1	11/2002	Keren et al.
2002/0177846	A1	11/2002	Mulier et al.
2002/0183682	A1	12/2002	Darvish et al.
2002/0183684	A1	12/2002	Dev et al.
2002/0188325	A1	12/2002	Hill et al.
2002/0198512	A1	12/2002	Seward
2003/0004549	A1	1/2003	Hill et al.
2003/0009145	A1	1/2003	Struijker-Boudier et al.
2003/0018367	A1	1/2003	DiLorenzo
2003/0040774	A1	2/2003	Terry et al.
2003/0045909	A1	3/2003	Gross et al.
2003/0050681	A1	3/2003	Pianca et al.
2003/0060848	A1	3/2003	Kieval et al.
2003/0060857	A1	3/2003	Perrson et al.
2003/0060858	A1	3/2003	Kieval et al.
2003/0082225	A1	5/2003	Mason
2003/0100924	A1	5/2003	Foreman et al.
2003/0120270	A1	6/2003	Acker
2003/0125790	A1	7/2003	Fastovsky et al.
2003/0150464	A1	8/2003	Casscells
2003/0158584	A1	8/2003	Cates et al.
2003/0181897	A1	9/2003	Thomas et al.
2003/0181963	A1	9/2003	Pellegrino et al.
2003/0199747	A1	10/2003	Michlitsch et al.
2003/0199767	A1	10/2003	Cespedes et al.
2003/0199768	A1	10/2003	Cespedes et al.
2003/0199806	A1	10/2003	Kieval
2003/0199863	A1	10/2003	Swanson et al.
2003/0204161	A1	10/2003	Ferek-Petric
2003/0216792	A1	11/2003	Levin et al.
2003/0220521	A1	11/2003	Reitz et al.
2003/0236443	A1	12/2003	Cespedes et al.
2004/0010289	A1	1/2004	Biggs et al.
2004/0010303	A1	1/2004	Bolea et al.
2004/0019364	A1	1/2004	Kieval et al.
2004/0019371	A1	1/2004	Jaafar et al.
2004/0064090	A1	4/2004	Keren et al.
2004/0064091	A1	4/2004	Keren et al.
2004/0065615	A1	4/2004	Hooper et al.
2004/0073238	A1	4/2004	Makower
2004/0082978	A1	4/2004	Harrison et al.
2004/0101523	A1	5/2004	Reitz et al.
2004/0106953	A1	6/2004	Yomtov et al.
2004/0111080	A1	6/2004	Harper et al.
2004/0127942	A1	7/2004	Yomtov et al.
2004/0162590	A1	8/2004	Whitehurst et al.
2004/0163655	A1	8/2004	Gelfand et al.
2004/0167415	A1	8/2004	Gelfand et al.
2004/0176699	A1	9/2004	Walker et al.
2004/0176757	A1	9/2004	Sinelnikov et al.
2004/0193228	A1	9/2004	Gerber
2004/0215186	A1	10/2004	Cornelius et al.
2004/0220511	A1	11/2004	Scott et al.
2004/0243102	A1	12/2004	Berg et al.
2004/0243206	A1	12/2004	Tadlock
2004/0249416	A1	12/2004	Yun et al.
2004/0254616	A1	12/2004	Rossing et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2005/0010263 A1 1/2005 Schauerte
2005/0021092 A1 1/2005 Yun et al.
2005/0038409 A1 2/2005 Segal et al.
2005/0049542 A1 3/2005 Sigg et al.
2005/0065562 A1 3/2005 Rezai
2005/0065573 A1 3/2005 Rezai
2005/0065574 A1 3/2005 Rezai
2005/0075681 A1 4/2005 Rezai et al.
2005/0080409 A1 4/2005 Young et al.
2005/0080459 A1 4/2005 Jacobson et al.
2005/0096710 A1 5/2005 Kieval
2005/0153885 A1 7/2005 Yun et al.
2005/0154418 A1 7/2005 Kieval et al.
2005/0171523 A1 8/2005 Rubinsky et al.
2005/0171574 A1 8/2005 Rubinsky et al.
2005/0171575 A1 8/2005 Dev et al.
2005/0187579 A1 8/2005 Danek et al.
2005/0192638 A1 9/2005 Gelfand et al.
2005/0197624 A1 9/2005 Goodson et al.
2005/0209548 A1 9/2005 Dev et al.
2005/0209642 A1 9/2005 Palti
2005/0228460 A1 10/2005 Levin et al.
2005/0234523 A1 10/2005 Levin et al.
2005/0240126 A1 10/2005 Foley et al.
2005/0240173 A1 10/2005 Palti
2005/0240228 A1 10/2005 Palti
2005/0240241 A1 10/2005 Yun et al.
2005/0245882 A1 11/2005 Elkins et al.
2005/0245892 A1 11/2005 Elkins et al.
2005/0251212 A1 11/2005 Kieval et al.
2005/0261672 A1 11/2005 Deem et al.
2005/0267010 A1 12/2005 Goodson et al.
2005/0282284 A1 12/2005 Rubinsky et al.
2006/0004417 A1 1/2006 Rossing et al.
2006/0004430 A1 1/2006 Rossing et al.
2006/0025821 A1 2/2006 Gelfand et al.
2006/0030814 A1 2/2006 Valencia et al.
2006/0036218 A1 2/2006 Goodson et al.
2006/0041277 A1 2/2006 Deem et al.
2006/0041283 A1 2/2006 Gelfand et al.
2006/0067972 A1 3/2006 Kesten et al.
2006/0069323 A1 3/2006 Elkins et al.
2006/0074453 A1 4/2006 Kieval et al.
2006/0079859 A1 4/2006 Elkins et al.
2006/0085046 A1 4/2006 Rezai et al.
2006/0089674 A1 4/2006 Walters et al.
2006/0095029 A1 5/2006 Young et al.
2006/0100667 A1 5/2006 Machado et al.
2006/0106429 A1 5/2006 Libbus et al.
2006/0111672 A1 5/2006 Seward
2006/0111754 A1 5/2006 Rezai et al.
2006/0116720 A1 6/2006 Knoblich
2006/0121016 A1 6/2006 Lee
2006/0121610 A1 6/2006 Rubinsky et al.
2006/0135998 A1 6/2006 Libbus et al.
2006/0136004 A1 6/2006 Cowan et al.
2006/0149350 A1 7/2006 Patel et al.
2006/0155344 A1 7/2006 Rezai et al.
2006/0167437 A1 7/2006 Valencia
2006/0167498 A1 7/2006 DiLorenzo
2006/0167499 A1 7/2006 Palti
2006/0189941 A1 8/2006 Seward et al.
2006/0189960 A1 8/2006 Kesten et al.
2006/0190044 A1 8/2006 Libbus et al.
2006/0206149 A1 9/2006 Yun
2006/0206150 A1 9/2006 Demarais et al.
2006/0212076 A1 9/2006 Demarais et al.
2006/0212078 A1 9/2006 Demarais et al.
2006/0229677 A1 10/2006 Moffitt et al.
2006/0235474 A1 10/2006 Demarais
2006/0265014 A1 11/2006 Demarais et al.
2006/0265015 A1 11/2006 Demarais et al.
2006/0271111 A1 11/2006 Demarais et al.
2006/0276852 A1 12/2006 Demarais et al.
2007/0066957 A1 3/2007 Demarais et al.
2007/0066959 A1 3/2007 Seward
2007/0066972 A1 3/2007 Ormsby et al.
2007/0078620 A1 4/2007 Seward et al.
2007/0083239 A1 4/2007 Demarais et al.
2007/0100318 A1 5/2007 Seward et al.
2007/0106249 A1 5/2007 Seward et al.
2007/0106250 A1 5/2007 Seward et al.
2007/0106251 A1 5/2007 Seward et al.
2007/0106255 A1 5/2007 Seward et al.
2007/0106256 A1 5/2007 Seward et al.
2007/0106257 A1 5/2007 Seward et al.
2007/0129720 A1 6/2007 Demarais et al.
2007/0129760 A1 6/2007 Demarais et al.
2007/0129761 A1 6/2007 Demarais et al.
2007/0135875 A1 6/2007 Demarais et al.
2007/0142864 A1 6/2007 Libbus et al.
2007/0156200 A1 7/2007 Kornet et al.
2007/0173899 A1 7/2007 Levin et al.
2007/0208382 A1 9/2007 Yun
2007/0265687 A1 11/2007 Deem et al.
2007/0269385 A1 11/2007 Yun et al.
2007/0282376 A1 12/2007 Shuros et al.
2007/0288070 A1 12/2007 Libbus et al.
2008/0004596 A1 1/2008 Yun et al.
2008/0004673 A1 1/2008 Rossing et al.
2008/0015659 A1 1/2008 Zhang et al.
2008/0039904 A1 2/2008 Bulkes et al.
2008/0045890 A1 2/2008 Seward et al.
2008/0091255 A1 4/2008 Caparso et al.
2008/0140150 A1 6/2008 Zhou et al.
2008/0213331 A1 9/2008 Gelfand et al.
2008/0255642 A1 10/2008 Zarins et al.
2008/0319513 A1 12/2008 Pu et al.
2009/0024195 A1 1/2009 Rezai et al.
2009/0036948 A1 2/2009 Levin et al.
2009/0062873 A1 3/2009 Wu et al.
2009/0076409 A1 3/2009 Wu et al.
2009/0142306 A1 6/2009 Seward et al.
2010/0010567 A1 1/2010 Deem et al.
2010/0057150 A1 3/2010 Demarais et al.
2010/0137860 A1 6/2010 Demarais et al.
2010/0137952 A1 6/2010 Demarais et al.
2010/0168731 A1 7/2010 Wu et al.
2010/0168739 A1 7/2010 Wu et al.
2010/0174282 A1 7/2010 Demarais et al.
2010/0191112 A1 7/2010 Demarais et al.
2010/0222851 A1 9/2010 Deem et al.
2010/0222854 A1 9/2010 Demarais et al.
2010/0249773 A1 9/2010 Clark et al.
2010/0268307 A1 10/2010 Demarais et al.
2011/0060324 A1 3/2011 Wu et al.
2011/0104060 A1 5/2011 Seward
2011/0104061 A1 5/2011 Seward
2011/0112400 A1 5/2011 Emery et al.
2011/0137298 A1 6/2011 Nguyen et al.
2011/0178570 A1 7/2011 Demarais
2011/0182912 A1 7/2011 Evans et al.
2011/0184337 A1 7/2011 Evans et al.
2011/0200171 A1 8/2011 Beetel et al.
2011/0202098 A1 8/2011 Demarais et al.
2011/0257564 A1 10/2011 Demarais et al.
2011/0264011 A1 10/2011 Wu et al.
2011/0264075 A1 10/2011 Leung et al.
2012/0172837 A1 7/2012 Demarais et al.
2012/0259269 A1 10/2012 Meyer
2012/0271277 A1 10/2012 Fischell et al.
2012/0271301 A1 10/2012 Fischell et al.
2013/0053792 A1 2/2013 Fischell et al.
2013/0053821 A1 2/2013 Fischell et al.
2013/0053822 A1 2/2013 Fischell et al.
2013/0172815 A1 7/2013 Perry et al.
2013/0204131 A1 8/2013 Seward
2013/0252932 A1 9/2013 Seward
2013/0274673 A1 10/2013 Fischell et al.
2013/0274674 A1 10/2013 Fischell et al.
2013/0287698 A1 10/2013 Seward
2013/0296853 A1 11/2013 Sugimoto et al.
2014/0012231 A1 1/2014 Fischell
2014/0046298 A1 2/2014 Fischell et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2014/0107478	A1	4/2014	Seward et al.
2014/0121641	A1	5/2014	Fischell et al.
2014/0121644	A1	5/2014	Fischell et al.
2014/0135661	A1	5/2014	Garrison et al.
2014/0236103	A1	8/2014	Fischell et al.
2014/0271717	A1	9/2014	Goshayeshgar et al.
2014/0276621	A1	9/2014	Braga
2014/0296279	A1	10/2014	Seward et al.
2014/0303569	A1	10/2014	Seward et al.
2014/0316351	A1	10/2014	Fischell et al.
2014/0358079	A1	12/2014	Fischell et al.
2014/0378906	A1	12/2014	Fischell et al.
2015/0005719	A1	1/2015	Fischell et al.

FOREIGN PATENT DOCUMENTS

EP	0233100		8/1987
EP	0774991		5/1997
EP	0811395		12/1997
EP	2092957		8/2009
EP	2352542		8/2011
EP	2429641		3/2012
EP	2528649		12/2012
EP	2656807		10/2013
EP	2675458		12/2013
EP	2694150		2/2014
EP	2747688		7/2014
JP	49009882		1/1974
JP	62181225	A	8/1987
JP	3041967		10/1997
JP	2004016333		1/2004
JP	2004503294		2/2004
WO	WO-85/01213		3/1985
WO	WO-91/04725		4/1991
WO	WO-9220291		11/1992
WO	WO-93/02740		2/1993
WO	WO-93/07803		4/1993
WO	WO-94/00188		1/1994
WO	WO-94/11057		5/1994
WO	WO-95/25472		9/1995
WO	WO-95/33514		12/1995
WO	WO-96/00039		1/1996
WO	WO-96/04957		2/1996
WO	WO-96/11723		4/1996
WO	WO-9641616		12/1996
WO	WO-97/13463		4/1997
WO	WO-97/13550		4/1997
WO	WO-9736548		10/1997
WO	WO-9742990		11/1997
WO	WO-97/49453		12/1997
WO	WO-98/37926		9/1998
WO	WO-98/42403		10/1998
WO	WO-98/43700		10/1998
WO	WO-98/43701		10/1998
WO	WO-98/48888		11/1998
WO	WO-99/33407		7/1999
WO	WO-99/51286		10/1999
WO	WO-99/52424		10/1999
WO	WO-01/26729		4/2001
WO	WO-0122897		4/2001
WO	WO-0170114		9/2001
WO	WO-0195832		12/2001
WO	WO-02/09808		2/2002
WO	WO-02/26314		4/2002
WO	WO-0226318		4/2002
WO	WO-02/053207		7/2002
WO	WO-02/070039		9/2002
WO	WO-02/070047		9/2002
WO	WO-02/085448		10/2002
WO	WO-02085192		10/2002
WO	WO-03/018108		3/2003
WO	WO-03024311		3/2003
WO	WO-03/028802		4/2003
WO	WO-03/063692		8/2003
WO	WO 03/071140		8/2003
WO	WO-03/076008		9/2003
WO	WO-03/082080		10/2003
WO	WO-03/082403		10/2003
WO	WO-2004/011055		2/2004
WO	WO-2004/026370		4/2004
WO	WO-2004/026371		4/2004
WO	WO-2004/026374		4/2004
WO	WO-2004/028583		4/2004
WO	WO-2004/030718		4/2004
WO	WO-2004/032791		4/2004
WO	WO-2004/107965		12/2004
WO	WO-2005/014100		2/2005
WO	WO-2005/016165		2/2005
WO	WO-2005/032646		4/2005
WO	WO-2005030072		4/2005
WO	WO-2005041748		5/2005
WO	WO-2005/065284		7/2005
WO	WO-2005/084389		9/2005
WO	WO-2005/097256		10/2005
WO	WO-2005/110528		11/2005
WO	WO-2005/123183		12/2005
WO	WO-2006/007048		1/2006
WO	WO-2006/018528		2/2006
WO	WO-2006/022790		3/2006
WO	WO-2006/031899		3/2006
WO	WO-2006041847		4/2006
WO	WO-2006041881		4/2006
WO	WO-2007008954		1/2007
WO	WO-2007035537		3/2007
WO	WO-2007078997		7/2007
WO	WO-2007086965		8/2007
WO	WO-2007103879		9/2007
WO	WO-2007103881		9/2007
WO	WO-2007121309		10/2007
WO	WO-2007146834		12/2007
WO	WO-2008003058		1/2008
WO	WO-2008061150		5/2008
WO	WO-2008061152		5/2008
WO	WO-2008070413		6/2008
WO	WO-2010078175		7/2010
WO	WO-2011094367		8/2011
WO	WO-2012161875		11/2012
WO	WO-2013028781		2/2013
WO	WO-2013059735		4/2013
WO	WO-2013/063331		5/2013
WO	WO-2013063331		5/2013
WO	WO-2013112844		8/2013
WO	WO-2013169741		11/2013
WO	WO-2013188689		12/2013
WO	WO-2014031167		2/2014
WO	WO-2014070820		5/2014
WO	WO-2014070999		5/2014
WO	WO-2014078301		5/2014
WO	WO-2014/189887		11/2014

OTHER PUBLICATIONS

2003 European Society of Hypertension—European Society of Cardiology guidelines for the management of arterial hypertension, Guidelines Committee, Journal of Hypertension 2003, vol. 21, No. 6, pp. 1011-1053.

Aars, H. and S. Akre, Reflex Changes in Sympathetic Activity and Arterial Blood Pressure Evoked by Afferent Stimulation of the Renal Nerve, Feb. 26, 1999, Acta physiol. Scand., vol. 78, 1970, pp. 184-188.

Abramov, G.S. et al., Alteration in sensory nerve function following electrical shock, Burns vol. 22, No. 8, 1996 Elsevier Science Ltd., pp. 602-606.

Achar, Suraj, M.D., and Suriti Kundu, M.D., Principles of Office Anesthesia: Part I. Infiltrative Anesthesia, Office Procedures, American Family Physician, Jul. 1, 2002, vol. 66, No. 1, pp. 91-94.

Advanced Neuromodulation Systems' Comparison Chart, Dec. 16, 2008, pp. 1.

Advances in the role of the sympathetic nervous system in cardiovascular medicine, 2001 SNS Report, No. 3, Springer, Published with an educational grant from Servier, pp. 1-8.

(56) **References Cited**

OTHER PUBLICATIONS

Aggarwal, A. et al., Regional sympathetic effects of low-dose clonidine in heart failure. Hypertension. 2003;41:553-7.
Agnew, William F. et al., Evolution and Resolution of Stimulation-Induced Axonal Injury in Peripheral Nerve, May 21, 1999, Muscle & Nerve, vol. 22, Oct. 1999, John Wiley & Sons, Inc. 1999, pp. 1393-1402.
Ahadian, Farshad M., M.D., Pulsed Radiofrequency Neurotomy: Advances in Pain Medicine, Current Pain and Headache Reports 2004, vol. 8, 2004 Current Science Inc., pp. 34-40.
Alexander, B.T. et al., Renal denervation abolishes hypertension in low-birth-weight offspring from pregnant rats with reduced uterine perfusion, Hypertension, 2005; 45 (part 2): pp. 754-758.
Alford, J. Winslow, M.D. and Paul D. Fadale, M.D., Evaluation of Postoperative Bupivacaine Infusion for Pain Management After Anterior Cruciate Ligament Reconstruction, The Journal of Arthroscopic and Related Surgery, vol. 19, No. 8, Oct. 2003 Arthroscopy Association of North America, pp. 855-861.
Allen, E.V., Sympathectomy for essential hypertension, Circulation, 1952, 6:131-140.
Amersham Health. Hypaque-Cysto, 2003, 6 pages.
Andrews, B.T. et al., The use of surgical sympathectomy in the treatment of chronic renal pain. Br J Urol. 1997; 80: 6-10.
Antman, Elliott M. and Eugene Braunwald, Chapter 37—Acute Myocardial Infarction, Heart Disease—A Textbook of Cardiovascular Medicine, 5th Edition, vol. 2, 1997, Edited by Eugene Braunwald, pp. 1184-1288.
Archer, Steffen et al., Cell Reactions to Dielectrophoretic Manipulation, Mar. 1, 1999, Biochemical and Biophysical Research Communications, 1999 Academic Press, pp. 687-698.
Arentz, T. et al., Incidence of pulmonary vein stenosis 2 years after radiofrequency catheter ablation of refractory atrial fibrillation. European Heart Journal. 2003. 24; pp. 963-969.
Arias, M.D., Manuel J., Percutaneous Radio-Frequency Thermocoagulation with Low Temperature in the Treatment of Essential Glossopharyngeal Neuralgia, Surg. Neurol. 1986, vol. 25, 1986 Elsevier Science Publishing Co., Inc., pp. 94-96.
Aronofsky, David H., D.D.S., Reduction of dental postsurgical symptoms using nonthermal pulsed high-peak-power electromagnetic energy, Oral Surg., Nov. 1971, vol. 32, No. 5, pp. 688-696.
Aspelin, Peter, M.D., Ph.D. et al., Nephrotoxic Effects in High-Risk Patients Undergoing Angiography, Feb. 6, 2003, New England Journal of Medicine 2003, vol. 348, No. 6, 2003 Massachusetts Medical Society, pp. 491-499.
Atrial Fibrillation Heart and Vascular Health on Yahoo! Health. 2 pgs. <URL: http://health.yahoo.com/topic/heart/overview/article/healthwise/hw160872;_ylt=AiBT43Ey74HQ7ft3jAb4C.sPu7cF> Feb. 21, 2006.
Augustyniak, Robert A. et al., Sympathetic Overactivity as a Cause of Hypertension in Chronic Renal Failure, Aug. 14, 2001, Journal of Hypertension 2002, vol. 20, 2002 Lippincott Williams & Wilkins, pp. 3-9.
Awwad, Ziad M., FRCS and Bashir A. Atiyat, GBA, JBA, Pain relief using continuous bupivacaine infusion in the paravertebral space after loin incision, May 15, 2004, Saudi Med J 2004, vol. 25 (10), pp. 1369-1373.
Badyal, D. K., H. Lata and A.P. Dadhich, Animal Models of Hypertension and Effect of Drugs, Aug. 19, 2003, Indian Journal of Pharmacology 2003, vol. 35, pp. 349-362.
Baker, Carol E. et al., Effect of pH of Bupivacaine on Duration of Repeated Sciatic Nerve Blocks in the Albino Rat, Anesth Analg, 1991, vol. 72, The International Anesthesia Research Society 1991, pp. 773-778.
Balazs, Tibor, Development of Tissue Resistance to Toxic Effects of Chemicals, Jan. 26, 1974, Toxicology, 2 (1974), Elsevier/North-Holland, Amsterdam, pp. 247-255.
Barajas, L. Innervation of the renal cortex. Fex Proc. 1978;37:1 192-201.
Barrett, Carolyn J. et al., Long-term control of renal blood flow: what is the role of the renal nerves?, Jan. 4, 2001, Am J Physiol Regulatory Integrative Comp Physiol 280, 2001, the American Physiological Society 2001, pp. R1534-R1545.
Barrett, Carolyn J. et al., What Sets the Long-Term Level of Renal Sympathetic Nerve Activity, May 12, 2003, Integrative Physiology, Circ Res. 2003, vol. 92, 2003 American Heart Association, pp. 1330-1336.
Bassett, C. Andrew L. et al., Augmentation of Bone Repair by Inductively Coupled Electromagnetic Fields, May 3, 1974, Science, vol. 184, pp. 575-577.
Bassett, C. Andrew L., Fundamental and Practical Aspects of Therapeutic Uses of Pulsed Electromagnetic Fields (PEMFs), Critical Reviews in Biomedical Engineering, vol. 17, Issue 5, 1989, pp. 451-514.
Beebe, Stephen J. et al., Nanosecond pulsed electric fields modulate cell function through intracellular signal transduction mechanisms, Apr. 8, 2004, Physiol. Meas. 25, 2004, IOP Publishing Ltd. 2004, pp. 1077-1093.
Beebe, Stephen J., et al., Nanosecond Pulsed Electric Field (nsPEF) Effects on Cells and Tissues: Apoptosis Induction and Tumor Growth Inhibition, Oct. 11, 2001, IEEE Transactions on Plasma Science, vol. 30, No. 1, Feb. 2002, IEEE 2002, pp. 286-292.
Bello-Reuss, E. et al., Acute unilateral renal denervation in rats with extracellular volume expansion, Departments of Medicine and Physiology, University of North Carolina School of Medicine. F26-F32 Jul. 1975.
Bello-Reuss, E. et al., Effect of renal sympathetic nerve stimulation on proximal water and sodium reabsorption, J Clin Invest, 1976;57:1104-1107.
Bello-Reuss, E. et al., Effects of Acute Unilateral Renal Denervation in the Rat, J Clin Invest, 1975;56:208-217.
Berde, C. et al., Local Anesthetics, Anesthesia, Chapter 13, 5th addition, Churchill-Livingston, Philadelphia 2000, pp. 491-521.
Bhadra, Niloy and Kevin L. Kilgore, Direct Current Electrical Conduction Block of Peripheral Nerve, Feb. 25, 2004, IEEE Transactions on Neural Systems and Rehabilitation Engineering, vol. 12, No. 3, Sep. 2004, pp. 313-324.
Bhandari, A. And Ellias, M., Loin pain hematuria syndrome: Pain control with RFA to the Splanchanic plexus, The Pain Clinic, 2000, vol. 12, No. 4, pp. 323-327.
Bhatt, Deepak L. et al., Rhabdomyolysis Due to Pulsed Electric Fields, May 11, 1989, Plastic and Reconstructive Surgery Jul. 1990, pp. 1-11.
Bichet, D., et al., Renal intracortical blood flow and renin secretion after denervation by 6-hydroxydopamine. Can J Physiol Pharmacol. 1982;60:184-92.
Bigler, D. et al., Tachyphylaxis during postoperative epidural analgesia—new insights, Apr. 15, 1987, Letter to the Editor, Acta Anaesthesiol Scand. 1987, vol. 31, pp. 664-665.
Binder, Allan et al., Pulsed Electromagnetic Field Therapy of Persistent Rotator Cuff Tendinitis, The Lancet, Saturday Mar. 31, 1984, The Lancet Ltd., pp. 695-698.
Black, M.D., Henry R., Resistant Hypertension 2004, presentation at Rush University Medical Center, Jul. 15, 2004, 40 pages.
Blad, B., et al., An Electrical Impedance index to Assess Electroporation in Tissue, Tissue and Organ (Therapy), 2001, Oslo, www.bl.uk <http://www.bl.uk> British Library, pp. 31-34.
Blair, M. L. et al, Sympathetic activation cannot fully account for increased plasma renin levels during water deprivation, Sep. 23, 1996, Am. J. Physiol., vol. 272, 1997, the American Physiological Society 1997, pp. R1197-R1203.
Blomberg, S.G., M.D., PhD, Long-Term Home Self-Treatment with High Thoracic Epidural Anesthesia in Patients with Severe Coronary Artery Disease, Mar. 29, 1994, Anesth Analg 1994, vol. 79, 1994 International Anesthesia Research Society, pp. 413-421.
Boehmer, J.P., Resynchronization Therapy for Chronic CHF: Indications, Devices and Outcomes. Penn State College of Medicine: Penn State Heart and Vascular Institute. Transcatheter Cardiovascular Therapeutics 2005, 31 slides.
Bourge, R.C., Heart Failure Monitoring Devices: Rationale and Status 28 pages, Feb. 2001.

(56) **References Cited**

OTHER PUBLICATIONS

Braunwald, E., Heart Disease, A Textbook of Cardiovascular Medicine, 5th Ed., vol. 2, 1997, pp. 480-481, 824-825, 1184-1288 and 1923-1925, W.B. Saunders Company.
Bravo, E.L., et al., Renal denervation for resistant hypertension, American Journal of Kidney Diseases, 2009, 3 pgs.
Bunch, Jared T. et al. Mechanisms of Phrenic Nerve Injury During Radiofrequency Ablation at the Pulmonary Vein Orifice. Journal of Cardiovascular Electrophysiclody. vol. 16, No. 12. pp. 1318-1325. Dec. 2005.
Burkhoff, D., Interventional Device-Based Therapy for CHF Will Redefine Current Treatment Paradigms. Columbia University. 2004. 32 slides.
Burns, J. et al., Relationship between central sympathetic drive and magnetic resonance imaging-determined left ventricular mass in essential hypertension. Circulation. 2007;115:1999-2005.
Cahana, A. et al., Acute Differential Modulation of Synaptic Transmission and Cell Survival During Exposure to Pulsed and Continuous Radiofrequency Energy, May 2003, The Journal of Pain, vol. 4, No. 4, © 2003 by the American Pain Society, pp. 197-202.
Cahana, Alex, M.D., Pulsed Radiofrequency: A Neurobiologic and Clinical Reality, May 17, 2005, Anesthesiology 2005, vol. 103, No. 6, Dec. 2005, 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc., p. 1311.
Calaresu, F.R. et al., Haemodynamic Responses and Renin Release During Stimulation of Afferent Renal Nerves in the Cat, Aug. 12, 1975, J. Physiol. 1976, vol. 255, pp. 687-700.
Cameron, Tracy. Micromodular Implants to Provide Electrical Stimulation of Paralyzed Muscles and Limbs. IEEE Transactions on Biomedical Engineering, vol. 44, No. 9, Sep. 1997. pp. 781-790.
Campese, V.M. et al., Renal afferent denervation prevents hypertension in rats with chronic renal failure. Hypertension. 1995;25:878-82.
Campese, V.M. et al., Renal Afferent Denervation Prevents the Progression of Renal Disease in the Renal Ablation Model of Chronic Renal Failure in the Rat, Am J Kidney Dis. 1995;26:861-5.
Campese, V.M., A new model of neurogenic hypertension caused by renal injury: pathophysiology and therapeutic implications, Clin Exp Nephrol (2003) 7: 167-171, Japanese Society of Nephrology 2003.
Campese, V.M., Neurogenic factors and hypertension in chronic renal failure, Journal of Nephrology, vol. 10, No. 4, 1997, Societa Italiana di Nefrologia, pp. 184-187.
Campese, V.M., Neurogenic factors and hypertension in renal disease. Kidney Int. 2000;57 Suppl 75:S2-3.
Canbaz, S. et al., Electrophysiological evaluation of phrenic nerve injury during cardiac surgery—a prospective, controlled clinical study. BioMed Central. 5 pgs. 2004.
Cardiac Glycosides, Heart Disease—A Textbook of Cardiovascular Medicine vol. 2, Edited by Eugene Braunwald, 5th Edition, 1997 WB Saunders Company, pp. 480-481.
Carls, G. et al., Electrical and magnetic stimulation of the intercostal nerves: a comparative study, Electromyogr, clin. Neurophysiol. 1997, vol. 37, pp. 509-512.
Carlson, Scott H. and J. Michael Wyss, e-Hypertension—Opening New Vistas, Introductory Commentary, Hypertension 2000, vol. 35, American Heart Association, Inc. 2000, p. 538.
Carson, P., Device-based Treatment for Chronic Heart Failure: Electrical Modulation of Myocardial Contractility. Transcatheter Cardiovascular Therapeutics 2005, 21 slides.
Chang, Donald C., Cell poration and cell fusion using an oscillating electric field, Biophysical Journal, vol. 56, Oct. 1989, Biophysical Society, pp. 641-652.
Chen, S.A. et al., Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablataion, Circulation, 1999, 100:1879-1886.
Chin, J.L. et al., Renal autotransplantation for the loin pain-hematuria syndrome: long term follow up of 26 cases, J Urol, 1998, vol. 160, pp. 1232-1236.
Chiou, C.W. et al., Efferent Vagal Innervation of the Canine Atria and Sinus and Atrioventricular Nodes. Circulation. Jun. 1997. 95(11):2573-2584. Abstract only. 2 pgs.
Chobanian, Aram V. et al., Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, Nov. 6, 2003, Hypertension 2003, vol. 42, 2003 American Heart Association, Inc., pp. 1206-1252.
Clinical Trials in Hypertension and Renal Diseases, Slide Source, www.hypertensiononline.org, 33 pages Aug. 13, 2001.
Conradi, E. and Ines Helen Pages, Effects of Continous and Pulsed Microwave Irradiation on Distribution of Heat in the Gluteal Region of Minipigs, Scand J Rehab Med, vol. 21, 1989, pp. 59-62.
Converse, R.L., Jr. et al., Sympathetic Overactivity in Patients with Chronic Renal Failure, N Engl J Med. Dec. 31, 1992, vol. 327 (27), pp. 1912-1918.
Cosman, E.R., Jr. et al., Electric and Thermal Field Effects in Tissue Around Radiofrequency Electrodes, Pain Medicine, vol. 6, No. 6, 2005, American Academy of Pain Medicine, pp. 405-424.
Cosman, E.R., Ph.D., A Comment on the History of the Pulsed Radiofrequency Technique for Pain Therapy, Anesthesiology Dec. 2005, vol. 103, No. 6, 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc., p. 1312.
Crawford, William H. et al., Pulsed Radio Frequency Therapy of Experimentally Induced Arthritis in Ponies, Dec. 18, 1989, Can. J. Vet. Res. 1991, vol. 55, pp. 76-85.
Curtis, J.J. et al., Surgical theray for persistent hypertension after renal transplantation, Transplantation, 1981, 31(2):125-128.
Dahm, Peter et al., Efficacy and Technical Complications of Long-Term Continuous Intraspinal Infusions of Opioid and/or Bupivacaine in Refractory Nonmalignant Pain . . . , Oct. 6, 1997, The Clinical Journal of Pain, vol. 14, No. 1, 1998, Lippincott-Raven Publishers 1998, pp. 4-16.
Dahm, Peter O. et al., Long-Term Intrathecal Infusion of Opioid and/or Bupivacaine in the Prophylaxis and Treatment of Phantom Limb Pain, Neuromodulation, vol. 1, No. 3, 1998, International Neuromodulation Society 1998, pp. 111-128.
Dang, Nicholas C. et al., A Novel Approach to Increase Total Urine Output in Heart Failure: Renal Nerve Blockade, ACC 2005 poster; 1 page.
Daniel, Alan and Honig, Carl R. Does Histamine Influence Vasodilation Caused by Prolonged Arterial Occlusion or Heavy Exercise? The Journal of Pharmacology and Experimental Therapeutics. vol. 215 No. 2. Aug. 21, 1980. pp. 533-538.
Davalos, R. et al., Electrical Impedance Tomography for Imaging Tissue Electroporation, Jul. 25, 2003, IEEE Transactions on Biomedical Engineering, vol. 51, No. 5, May 2004, IEEE 2004, pp. 761-767.
Davalos, R.V. et al., Tissue Ablation with Irreversible Electroporation, Sep. 7, 2004, Annals of Biomedical Engineering, Feb. 2005, vol. 33, No. 2, 2005 Biomedical Engineering Society, pp. 223-231.
De Leeuw, Peter W. et al., Renal Vascular Tachyphylaxis to Angiotensin II: Specificity of the Response for Angiotensin, Dec. 28, 1981, Life Sciences, vol. 30, 1982 Pergamon Press Ltd., pp. 813-819.
Deng, Jingdong et al., The Effects of Intense Submicrosecond Electrical Pulses on Cells, Nov. 26, 2002, Biophysical Journal, vol. 84, Apr. 2003, Biophysical Society 2003, pp. 2709-2714.
Denton, Kate M. et al., Differential Neural Control of Glomerular Ultrafiltration, Jan. 30, 2004, Proceedings of the Australian Physiological and Pharmacological Society Symposium: Hormonal, Metabolic and Neural Control of the Kidney, Clinical and Experimental Pharmacology and Physiology (2004) 31, pp. 380-386.
Dev, Nagendu B., Ph.D. et al., Intravascular Electroporation Markedly Attenuates Neointima Formation After Balloon Injury of the Carotid Artery in the Rat, Journal of Interventional Cardiology, vol. 13, No. 5, 2000, pp. 331-338.
Dev, Nagendu B., Ph.D. et al., Sustained Local Delivery of Heparin to the Rabbit Arterial Wall with an Electroporation Catheter, May 5, 1998, Catheterization and Cardiovascular Diagnosis, vol. 45, 1998, Wiley-Liss, Inc. 1998, pp. 337-345.
Devereaux, R.B. et al., Regression of Hypertensive Left Ventricular Hypertrophy by Losartan Compared With Atenolol: The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial, Circulation, 2004, vol. 110, pp. 1456-1462.

(56) **References Cited**

OTHER PUBLICATIONS

Dibona, Gerald F. and Linda L. Sawin, Role of renal nerves in sodium retention of cirrhosis and congestive heart failure, Sep. 27, 1990, Am. J. Physiol. 1991, vol. 260, 1991 the American Physiological Society, pp. R298-R305.
Dibona, Gerald F. and Susan Y. Jones, Dynamic Analysis of Renal Nerve Activity Responses to Baroreceptor Denervation in Hypertensive Rats, Sep. 19, 2000, Hypertension Apr. 2001, American Heart Association, Inc. 2001, pp. 1153-1163.
Dibona, Gerald F. and Ulla C. Kopp, Neural Control of Renal Function, Physiological Reviews, vol. 77, No. 1, Jan. 1997, the American Physiological Society 1997, pp. 75-197.
Dibona, Gerald F. and Ulla C. Kopp, Role of the Renal Sympathetic Nerves in Pathophysiological States, Neural Control of Renal Function, vol. 77, pp. 142-197 Jan. 1997.
Dibona, Gerald F., Functionally Specific Renal Sympathetic Nerve Fibers: Role in Cardiovascular Regulation, Mar. 6, 2001, American Journal of Hypertension, 2001, vol. 14, 2001 American Journal of Hypertension, Ltd. Published by Elsevier Science Inc., pp. 163S-170S.
Dibona, Gerald F., L.L. Sawin, Effect of renal nerve stimulation on NaCl and H2O transport in Henle's loop of the rat,: 1982, American Physiological Society, F576-F580, 5 pgs.
Dibona, Gerald F., Nervous Kidney—Interaction Between Renal Sympathetic Nerves and the Renin-Angiotensin System in the Control of Renal Function, Jun. 21, 2000, Hypertension 2000, vol. 36, 2000 American Heart Association, Inc., pp. 1083-1088.
Dibona, Gerald F., Neural Control of the Kidney—Past, Present and Future, Nov. 4, 2002, Novartis Lecture, Hypertension 2003, 41 part 2, 2002 American Heart Association, Inc., pp. 621-624.
DiBona, Gerald F., Neural Control of the Kidney: Functionally Specific Renal Sympathetic Nerve Fibers, Starling Lecture, Am J Physiol Regulatory Integrative Comp Physiol, 2000, 279, 2000 The American Physiological Society, pp. R1517-R1524.
Dibona, Gerald F., Peripheral and Central Interactions between the Renin-Angiotensin System and the Renal Sympathetic Nerves in Control of Renal Function, Annals New York Academy of Sciences, pp. 395-406 Jan. 25, 2006.
Dibona, Gerald F., Renal Innervation and Denervation: Lessons from Renal Transplantation Reconsidered, Artificial Organs, vol. 11, No. 6, Raven Press, Ltd., 1987 International Society for Artificial Organs, pp. 457-462.
Dibona, Gerald F., Sympathetic Nervous System and the Kidney in Hypertension, Current Opinion in Nephrology and Hypertension 2002, vol. 11, 2002 Lippincott Williams & Wilkins, pp. 197-200.
Dibona, Gerald F., The Sympathetic Nervous System and Hypertension, Dec. 4, 2003, Hypertension Highlights, Hypertension Feb. 2004, vol. 43, 2004 American Heart Association, Inc., pp. 147-150.
Dibona, Gerald, LL Sawin, Effect of renal denervation on dynamic autoregulation of renal blood flow, Feb. 12, 2004, AmJ Physiol Renal Physiol 286, pp. F1209-1218.
Dong, Jun et al. Incidence and Predictors of Pulmonary Vein Stenosis Following Catheter Ablation of Atrial Fibrillation Using the Anatomic Pulmonary Vein Ablation Approach: Results from Paired Magnetic Resonance Imaging. Journal of Cardiovascular Electrophysiology. vol. 16, No. 8, Aug. 2005. pp. 845-852.
Dorros, Gerald, M.D., Renal Artery Stenting State of the Art, presentation, TCT, Washington D.C., Sep. 2003, 27 pages.
Dueck, Ron, M.D., Noninvasive Cardiac Output Monitoring, The Cardiopulmonary and Critical Care Journal, Chest, vol. 120, sec. 2, Aug. 2001, American College of Chest Physicians 2005, pp. 339-341, 5 pages.
Dunn, Matthew D. et al., Laparoscopic Nephrectomy in Patients With End-Stage Renal Disease and Autosomal Dominant Polycystic Kidney Disease,Oct. 25, 1999, American Journal of Kidney Diseases, vol. 35, No. 4 Apr. 2000, National Kidney Foundation, Inc. 2000, pp. 720-725.
Durand, D.M., Electric Field Effects in Hyperexcitable Neural Tissue: A Review, Radiation Protection Dosimetry, vol. 106, No. 4, 2003 Nuclear Technology Publishing, pp. 325-331.
Effects of Renal Failure on the Cardiovascular System, 5th Edition Heart Disease, A Textbook of Cardiovascular Medicine, vol. 2, Edited by Eugene Braunwald, 1997, W.B. Saunders Company, pp. 1923-1925.
Electrical Stimulation for the Treatment of Chronic Wounds, Radiation Protection Standard, Maximum Exposure Levels to Radiofrequency Fields—3 KHz to 300 GHz, Radiation Protection Series No. 3, Australian Radiation Protection and Nuclear Safety Agency, Apr. 1996, 322 pgs.
Electropermeabilization (Electroporation), Cyto Pulse Sciences, Inc., http://www.cytopulse.com/electroporation.html (last accessed Mar. 3, 2005), 3 pgs.
Electroporation based Technologies and Treatments, ESPE Newsletter No. 6, QLK 02002-2003, Jan. 2005, www.cliniporator.com, 4 pgs.
End-stage renal disease payment policies in traditional Medicare, Chapter 8, Report to the Congress: Medicare Payment Policy, Mar. 2001, Medpac, pp. 123-138.
Epidemiology of Renal Disease in Hypertension, slide presentation by hypertensiononline.org, 21 pages Mar. 30, 2001.
Erdine, Serap and Alev Arat-Ozkan, Resistant Hypertension, European Society of Hypertension Scientific Newsletter: Update on Hypertension Management 2003, vol. 4, No. 15, 2 pages.
Esler, M. et al., Mechanism of elevated plasma noradrenaline in the course of essential hypertension. J Cardiovasc Pharmacol. 1986;8:S39-43.
Esler, M. et al., Noradrenaline release and the pathophysiology of primary human hypertension. Am J Hypertens. 1989; 2:140S-146S.
Esler, M. et al., Sympathetic nerve biology in essential hypertension, Clin and Exp Pharmacology and Physiology, 2001, 28:986-989.
European Examination Report; European Patent Application No. 07799148.7; Applicant: Ardian, Inc.; Date of Mailing: Jan. 19, 2010, 4 pgs.
European Examination Report; European Patent Application No. 09156661.2; Applicant: Ardian, Inc.; Date of Mailing: Jan. 19, 2010, 6 pgs.
European Search Report; European Patent Application No. 05806045.0; Applicant: Ardian, Inc.; Date of Mailing: Aug. 22, 2009, 8 pgs.
European Search Report; European Patent Application No. 05811851.4; Applicant: Ardian, Inc.; Date of Mailing: Oct. 1, 2009, 7 pgs.
European Search Report; European Patent Application No. 06847926.0; Applicant: Ardian, Inc.; Date of Mailing: Feb. 10, 2010, 6 pgs.
European Search Report; European Patent Application No. 07757925.8; Applicant: Ardian, Inc.; Date of Mailing: Apr. 29, 2010, 9 pgs.
European Search Report; European Patent Application No. 07798341.9; Applicant: Ardian, Inc.; Date of Mailing Aug. 4, 2011; 6 pgs.
European Search Report; European Patent Application No. 07799148.7; Applicant: Ardian, Inc.; Date of Mailing: Jul. 23, 2009, 6 pgs.
European Search Report; European Patent Application No. 07868755.5; Applicant: Ardian, Inc.; Date of Mailing: Jul. 28, 2010, 7 pgs.
European Search Report; European Patent Application No. 09156661.2; Applicant: Ardian, Inc.; Date of Mailing: Jul. 23, 2009, 6 pgs.
European Search Report; European Patent Application No. 09167937.3; Applicant: Ardian, Inc.; Date of Mailing: Nov. 11, 2009, 6 pgs.
European Search Report; European Patent Application No. 09168202.1; Applicant: Ardian, Inc.; Date of Mailing: Nov. 11, 2009, 5 pgs.
European Search Report; European Patent Application No. 09168204.7; Applicant: Ardian, Inc.; Date of Mailing: Nov. 19, 2009, 6 pgs.
Evelyn, K.A. et al., Effect of thoracolumbar sympathectomy on the clinical course of primary (essential) hypertension, Am J Med, 1960;28:188-221.
Ex parte Quayle Office Action; U.S. Appl. No. 11/144,173; Mailed on May 28, 2009, 4 pgs.

(56) **References Cited**

OTHER PUBLICATIONS

Fact Book Fiscal Year 2003, National Institutes of Health National Heart, Lung, and Blood Institute, Feb. 2004, 197 pgs.
Fajardo, J. et al., Effect of chemical sympathectomy on renal hydroelectrolytic handling in dogs with chronic caval constriction. Clin Physiol Biochem. 1986;4:252-6.
Fareed, Jawed, Ph.D. et al., Some Objective Considerations for the Use of Heparins and Recombinant Hirudin in Percutaneous Transluminal Coronary Angoplasty, Seminars in Thrombosis and Hemostasis 1991, vol. 17, No. 4, 1991 by Thieme Medical Publishers, Inc., pp. 455-470.
Ferguson, D.R. et al., Responses of the pig isolated renal artery to transmural electrical stimulation and drugs, Dec. 7, 1984, Br. J. Pharmac. 1985, vol. 84, The Macmillan Press Ltd. 1985, pp. 879-882.
Fernandez-Ortiz, Antonio, et al., A New Approach for Local Intravascular Drug Delivery—Iontophoretic Balloon, Intravascular Iontophoretic Local Delivery, Circulation, vol. 89, No. 4, Apr. 1994, pp. 1518-1522.
Fields, Larry E. et al., The Burden of Adult Hypertension in the United States 1999 to 2000—A Rising Tide, May 18, 2004, American Heart Association 2004, Hypertension Oct. 2004, pp. 1-7.
Final Office Action; U.S. Appl. No. 11/233,814; Mailed on Jan. 29, 2009, 11 pgs.
Final Office Action; U.S. Appl. No. 11/266,993; Mailed on Jan. 8, 2010, 7 pgs.
Final Office Action; U.S. Appl. No. 11/363,867; Mailed on May 1, 2009, 8 pgs.
Final Office Action; U.S. Appl. No. 11/451,728; Mailed on Jan. 13, 2009, 7 pgs.
Final Office Action; U.S. Appl. No. 11/599,649; Mailed on Jan. 15, 2009, 10 pgs.
Final Office Action; U.S. Appl. No. 11/599,723; Mailed on Apr. 5, 2010, 17 pgs.
Final Office Action; U.S. Appl. No. 11/599,890; Mailed on Apr. 29, 2009, 9 pgs.
Fischell, Tim A. et al., Ultrasonic Energy: Effects on Vascular Function and Integrity, Circulation: Journal of the American Heart Association. 1991. 84;pp. 1783-1795.
Freeman, Scott A. et al., Theory of Electroporation of Planar Bilayer Membranes: Predictions of the Aqueous Area, Change in Capacitance, and Pore-Pore Separation, Feb. 23, 1994, Biophysical Journal, Jul. 1994, vol. 67, 1994 by the Biophysical Society, pp. 42-56.
Fukuoka, Yuko et al., Imaging of neural conduction block by neuromagnetic recording, Oct. 16, 2002, Clinical Neurophysiology, vol. 113, 2002, Elsevier Science Ireland Ltd. 2002, pp. 1985-1992.
Fuster, Valentin et al. ACC/AHA/ESC Practice Guidelines: ACA/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. JACC vol. 48, No. 4, Aug. 15, 2006.
Gami, Apoor S., M.D. and Vesna D. Garovic, M.D., Contrast Nephropathy After Coronary Angiography, Mayo Clin Proc. 2004, vol. 79, 2004 Mayo Foundation for Medical Education and Research, pp. 211-219.
Gattone II, Vincent H. et al., Contribution of Renal Innervation to Hypertension in Polycystic Kidney Disease in the Rat, University of Chicago Section of Urology, 16 pages, Mar. 17, 2008.
Gaylor, D.C. et al., Significance of Cell Size and Tissue Structure in Electrical Trauma, Jan. 26, 1988, J. theor. Biol. 1988, vol. 133, 1988 Academic Press Limited, pp. 223-237.
Gazdar, A.F. and G.J. Dammin, Neural degeneration and regeneration in human renal transplants, NEJM, Jul. 30, 1970, 283:222-244.
Gehl, Julie et al., In Vivo Electroporation of Skeletal Muscle: Threshold, Efficacy and Relation to Electric Field Distribution, Biochimica et Biophysica Acta, 1428, 1999, Elsevier Science B.V. 1999, pp. 233-240, www.elsevier.com/locate/bba <http:www.elsevier.com/locate/bba>.
Getts, R.T. et al., Regression of left ventricular hypertrophy after bilateral nephrectomy, Nephrol Dial Transplant, 2006, vol. 21, pp. 1089-1091.
Ghoname, El-sayed A. et al., Percutaneous electrical nerve stimulation: an alternative to TENS in the management of sciatica, Apr. 26, 1999, Pain 1999, vol. 83, 1999 International Association for the Study of Pain / Published by Elsevier Science B.V., pp. 193-199.
Gimple, M.D., Lawrence et al., Effect of Chronic Subcutaneous or Intramural Administration of Heparin on Femoral Artery Restenosis After Balloon Angioplasty in Hypercholesterolemic Rabbits, Laboratory Investigation, Circulation, vol. 86, No. 5, Nov. 1992, pp. 1536-1546.
Goldberger, Jeffrey J. et al., New technique for vagal nerve stimulation, Jun. 2, 1999, Journal of Neuroscience Methods 91, 1999, Elsevier Science B.V. 1999, pp. 109-114.
Gorbunov, F.E. et al., The Use of Pulsed and Continuous Short Wave Diathermy (Electric Field) in Medical Rehabilitation of the Patients with Guillan-Barre Syndrome and Other Peripheral Myelinopathies, May 6, 1994, 5 pages (most of article in Russian language).
Gottschalk, C.W., Renal nerves and sodium excretion, Ann. Rev. Physiol., 1979, 41:229-240.
Greenwell, T.J. et al., The outcome of renal denervation for managing loin pain haematuria syndrome. BJU International, 2004; 4 pgs.
Gruberg, Luis, M.D. et al., The Prognostic Implications of Further Renal Function Deterioration Within 48 h of Interventional Coronary Procedures in Patients with Pre-existent Chronic Renal Insufficiency, Jun. 19, 2000, Journal of the American College of Cardiology 2000, vol. 36, No. 5, 2000 by the American College of Cardiology, pp. 1542-1548.
Guimaraes, Sarfim. Vascular Adrenoceptors: An Update. pp. 319-356, Jun. 1, 2001.
Haissaguerre, M. et al., Spontaneous initiation of atrial fibrillation by ectopic beats orginating in the pulmonary veins, New England Journal of Medicine, 1998, 339: 659-666.
Hajjar, Ihab, M.D., M.S. and Theodore A. Kotchen, M.D., Trends in Prevalence, Awareness, Treatment, and Control of Hypertension in the United States, 1988-2000, JAMA, Jul. 9, 2003, vol. 290, No. 2, pp. 199-206.
Hammer, Leah W. Differential Inhibition of Functional Dilation of Small Arterioles by Indomethacin and Glibenclamide. Hypertension. Feb. 2001 Part II. pp. 599-603.
Hampers, C.L. et al., A hemodynamic evaluation of bilateral nephrectomy and hemodialysis in hypertensive man, Circulation. 1967;35:272-288.
Hamza, M.D., Mohamed A. et al., Effect of the Duration of Electrical Stimulation on the Analgesic Response in Patients with Low Back Pain, Anesthesiology, vol. 91, No. 6, Dec. 1999, American Society of Anesthesiologists, Inc. 1999, pp. 1622-1627.
Han, Hyo-Kyung and Gordon L. Amidon, Targeted Prodrug Design to Optimize Drug Delivery, Mar. 21, 2000, AAPS Pharmsci 2000, 2 (1) article 6, pp. 1-11.
Hansen, J.M. et al., The transplanted human kidney does not achieve functional reinnervation, Clin Science, 1994, vol. 87, pp. 13-20.
Hasking, G.J. et al., Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation. 1986;73:615-21.
Hausberg, M. et al., Sympathetic nerve activity in end-stage renal disease, Circulation, 2002, 106: 1974-1979.
Heart Arrhythmia Heart and Vascular Health on Yahoo! Health. 13 pgs. <URL: http://health.yahoo.com/topic/heart/overview/article/mayoclinic/21BBE2B0-128D-4AA2-A5CE215065586678;_ylt=Aqd9M5rNyHDOsbPOmHXFhLcPu7cF> Feb. 16, 2005.
Heart Disease and Stroke Statistics—2004 Update, American Heart Association, American Stroke Association, Dallas, Texas, 2003 American Heart Association, 52 pgs.
Heida, Tjitske, et al., Investigating Membrane Breakdown of Neuronal Cells Exposed to Nonuniform Electric Fields by Finite-Element Modeling and Experiments, May 9, 2002, IEEE Transactions on Biomedical Engineering, vol. 49, No. 10, Oct. 2002, IEEE 2002, pp. 1195-1203.
Heuer, G.J., The surgical treatment of essential hypertension, Annals of Surgery, 1936; 104(4): 771-786.
Higuchi, Yoshinori, M.D., Ph.D. et al, Exposure of the Dorsal Root Ganglion in Rats to Pulsed Radiofrequency Currents Activates Dorsal Horn Lamina I and II Neurons, Dec. 4, 2001, Experimental Studies, Neurosurgery, vol. 50, No. 4, Apr. 2002, pp. 850-856.

(56) **References Cited**

OTHER PUBLICATIONS

Hildebrand, Keith R., D.V.M., Ph.D. et al., Stability, Compatibility, and Safety of Intrathecal Bupivacaine Administered Chronically via an Implantable Delivery System, May 18, 2001, The Clinical Journal of Pain, vol. 17, No. 3, 2001 Lippincott Williams & Wilkins, Inc., pp. 239-244.
Hing, Esther, M.P.H. and Kimberly Middleton, B.S.N., M.P.H., National Hospital Ambulatory Medical Care Survey: 2001 Outpatient Department Summary, Aug. 5, 2003, Advance Data from Vital and Health Statistics, No. 338, CDC, 32 pages.
Hodgkin, Douglas D. et al., Electrophysiologic Characteristics of a Pulsed Iontophoretic Drug-Delivery System in Coronary Arteries, Journal of Cardiovascular Pharmacology. 29(1):pp. 39-44, Jan. 1997, Abstract, 2 pgs.
Hopp, F.A. et al., Respiratory Responses to Selective Blockade of Carotid Sinus Baroreceptors in the Dog, Jun. 22, 2005, Am J Physiol Regul Integr Comp Physiol 1998, vol. 275, 2005 American Physiological Society, pp. R10-R18.
Hortobagyi, Gabriel N., Randomized Trial of High-Dose Chemotherapy and Blood Cell Autographs for High-Risk Primary Breast Carcinoma, Journal of the National Cancer Institute, vol. 92, No. 3, Feb. 2, 2000, pp. 225-233.
Horwich, Tamara, M.D., New Advances in the Diagnosis and Management of Acute Decompensated Heart Failure, the heart.org satellite program, Rapid Review, CME Symposium presented on Nov. 8, 2004 at the Sheraton New Orleans Hotel, 4 pages.
Huang, Wann-Chu et al. Renal Denervation Prevents and Reverses Hyperinsulinemia-Induced Hypertension in Rats, Mar. 25, 1998, Hypertension 1998, vol. 32, 1998 American Heart Association, pp. 249-254.
Huang, Yifei et al., Remodeling of the chronic severely failing ischemic sheep heart after coronary microembolization: functional, energetic, structural and cellular responses, Jan. 8, 2004, Am J Physiol. Heart Circ. Physiol. 2004, vol. 286, 2004 the American Physiological Society, pp. H2141-H2150.
Hughes, Gordon B., M.D. et al., A Comparative Study of Neuropathologic Changes Following Pulsed and Direct Current Stimulation of the Mouse Sciatic Nerve, Jun. 27, 1980, American Journal of Otolaryngology, Nov. 1980, vol. 1, No. 5, pp. 378-384.
Hypertension and Renal Disease: Mechanisms, Slide Show by www.hypertensiononline.org, 22 pages Mar. 30, 2001.
Hypertension Incidence and Prevalence, Age-Specific Rates, by Gender, B.C., 2001/2002, Graph, Chronic Disease Management, May 2003, British Columbia Ministry of Health Services, 1 page.
Implantable Neurostimulation Systems, Medtronic Neurological, Jan. 18, 1999, 6 pages. http://medtronic.com/neuro/paintherapies/pain_treatment_ladder/pdf/implantable_brochure.pdf.
Implantable Pump—The Medtronic MiniMed 2007 Implantable Insulin Pump System, Medtronic MiniMed 2004, 4 pgs.
International Search Report and Written Opinion for PCT/US2009/069334; Applicant: Ardian, Inc.; Mailing Date: Mar. 1, 2010, 10 pgs.
International Search Report and Written Opinion, PCT/US05/35693, Mailed on Mar. 8, 2006, Applicant: Ardian, Inc., 29 pgs.
International Search Report and Written Opinion, PCT/US05/35757, Mailed on Dec. 27, 2006, Applicant: Ardian, Inc., 8 pgs.
International Search Report and Written Opinion, PCT/US06/36120, Mailed on Jun. 25, 2008, Applicant: Ardian, Inc., 10 pgs.
International Search Report and Written Opinion, PCT/US06/41889, Mailed on Oct. 20, 2008, Applicant: Ardian, Inc., 7 pgs.
International Search Report and Written Opinion, PCT/US06/48822, Mailed on Aug. 15, 2008, Applicant: Ardian, Inc., 12 pgs.
International Search Report and Written Opinion, PCT/US07/633222, Mailed on Mar. 3, 2008, Applicant: Ardian, Inc., 10 pgs.
International Search Report and Written Opinion, PCT/US07/63324, Mailed on Oct. 10, 2008, Applicant: Ardian, Inc., 10 pgs.
International Search Report and Written Opinion, PCT/US07/66539, Mailed on Jan. 28, 2008, Applicant: Ardian, Inc., 6 pgs.
International Search Report and Written Opinion, PCT/US07/70799, Mailed on Jul. 2, 2008, Applicant: Ardian, Inc., 7 pgs.
International Search Report and Written Opinion, PCT/US07/72396, Mailed on Aug. 27, 2008, Applicant: Ardian, Inc., 9 pgs.
International Search Report and Written Opinion, PCT/US07/84701, Mailed on Aug. 21, 2008, Applicant: Ardian, Inc., 11 pgs.
International Search Report and Written Opinion, PCT/US07/84705, Mailed on Jul. 28, 2008, Applicant: Ardian, Inc., 12 pgs.
International Search Report and Written Opinion, PCT/US07/84708, Mailed on Aug. 11, 2008, Applicant: Ardian, Inc., 9 pgs.
International Search Report, PCT/US02/0039, Mailed Sep. 11, 2002, Applicant: Advanced Neuromodulation Systems, Inc.
International Search Report, PCT/US02/25712, Mailed on Apr. 23, 2003, Applicant: Cyberonics, Inc.
International Search Report, PCT/US03/08014, Mailed on Sep. 23, 2003, Applicant: The General Hospital Corporation.
International Search Report, PCT/US03/09764, Mailed on Oct. 28, 2003, Applicant: CVRX, Inc.
International Search Report, PCT/US04/38498, Mailed Feb. 18, 2005, Applicant: G & L Consulting, LLC, 4 pgs.
Introduction to Autonomic Pharmacology, Chapter 3, Part 2 Autonomic Pharmacology, pp. 18-26, May 24, 2002.
Isovue: Data Sheet. Regional Health Limited. 8 pgs. Mar. 11, 2003.
Israili, Z.H., Clinical pharmacokinetics of angiotensin II (AT) receptor blockers in hypertension, Journal of Human Hypertension, 2000, Macmillan Publishers Ltd., vol. 14, pp. S73-S86.
Janda, J., Impact of the electrical stimulation apparatus rebox on the course of ischemic renal damage in rats, British Library—The world's knowledge pp. 252-254 (translated and untranslated versions) 1996.
Janssen, Ben J.A. et al., Effects of complete renal denervation and selective afferent renal denervation on the hypertension induced by intrarenal norepinephrine infusion in conscious rats, Jan. 4, 1989, Journal of Hypertension 1989, vol. 7, No. 6, Current Science Ltd, pp. 447-455.
Jia, Jianping et al., Cold injury to nerves is not due to ischaemia alone, Brain. 121;pp. 989-1001. 1998.
Jia, Jianping et al.., The pathogenesis of non-freezing cold nerve injury: Observations in the rat, Brain. 120; pp. 631-646. 1997.
Jin, Yuanzhe et al., Pulmonary Vein Stenosis and Remodeling After Electrical Isolation for Treatment of Atrial Fibrillation: Short- and Medium-Term Follow-Up, PACE, vol. 27., Oct. 2004, pp. 1362-1370.
Johansson, Bjorn, Electrical Membrane Breakdown, A Possible Mediator of the Actions of Electroconvulsive Therapy, Medical Hypotheses 1987, vol. 24, Longman Group UK Ltd 1987, pp. 313-324.
Joles, J.A. et al., Causes and Consequences of Increased Sympathetic Activity in Renal Disease. Hypertension. 2004;43:699-706.
Jorgensen, William A. et al., Electrochemical Therapy of Pelvic Pain: Effects of Pulsed Electromagnetic Fields (PEMF) on Tissue Trauma, Eur J Surg 1994, Suppl 574, vol. 160, 1994 Scandinavian University Press, pp. 83-86.
Joshi, R. P. and K. H. Schoenbach, Mechanism for membrane electroporation irreversibility under high-intensity, ultrashort electrical pulse conditions, Nov. 11, 2002, Physical Review E 66, 2002, The American Physical Society 2002, pp. 052901-1-052901-4.
Joshi, R. P. et al., Improved energy model for membrane electroporation in biological cells subjected to electrical pulses, Apr. 9, 2002, Physical Review E, vol. 65, 041920-1, 2002 The American Physical Society, 8 pages.
Joshi, R. P. et al., Self-consistent simulations of electroporation dynamics in biological cells subjected to ultrashort electrical pulses, Jun. 21, 2001, Physical Review E, vol. 64, 011913, 2001 The American Physcial Society, pp. 1-10.
Joye, James D.et al., In Vivo Study of Endovascular Cryotherapy for the Prevention of Restenosis, 4 pages, 2003.
Kanduser, Masa et al., Effect of surfactant polyoxyethylene glycol (C12E8) on electroporation of cell line DC3F, Aug. 20, 2002, Colloids and Surfaces A: Physicochem. Eng. Aspects 214, 2003, Elsevier Science B.V. 2002, pp. 205-217.
Kassab, S. et al., Renal denervation attenuates the sodium retention and hypertension associated with obesity, Hypertension, 1995, 25:893-897.

(56) **References Cited**

OTHER PUBLICATIONS

Katholi, R.E. et al., Importance of the renal nerves in established two-kidney, one clip Goldblatt hypertension, Hypertension, 1982, 4 (suppl II):II-166-II-174.
Katholi, R.E. et al., Role of the renal nerves in the pathogenesis of one-kidney renal hypertension in the rat, Hypertension, 1981, 3(4) 404-409.
Katholi, R.E., Renal nerves and hypertension: an update, Fed Proc., 1985, 44:2846-2850.
Katholi, Richard E., Renal nerves in the pathogenesis of hypertension in experimental animals and humans, Am. J. Physiol. vol. 245, 1983, the American Physiological Society 1983, pp. F1-F14.
Kaye, D.M. et al., Functional and neurochemical evidence for partial cardiac sympathetic reinnervation after cardiac transplantation in humans, Circulation, 1993, vol. 88, pp. 1101-1109.
Kelleher, Catherine L. et al., Characteristics of Hypertension in Young Adults with Autosomal Dominant Polycystic Kidney Disease Compared with the General U.S. Population, Jun. 9, 2004, American Journal of Hypertension 2004, pp. 1029-1034.
King, Ronald W. P., Nerves in a Human Body Exposed to Low-Frequency Electromagnetic Fields, Jun. 7, 1999, IEEE Transactions on Biomedical Engineering, vol. 46, No. 12, Dec. 1999, IEEE 1999, pp. 1426-1431.
Kinney, Brian M., M.D., High-Tech Healing—The evolution of therapeutic electromagnetic fields in plastic surgery, Plastic Surgery Products, Jun. 2004, pp. 32-36, 3 pages.
Kirchheim, H. et al., Sympathetic modulation of renal hemodynamics, renin release and sodium excretion, Klin Wochenschr, 1989, 67:858-864.
Klein, K. et al., Impaired autofeedback regulation of hypothalamic norepinephrine release in experimental uremia. J Am Soc Nephrol. 2005;16:2081-7.
Knot, H. J. et al., Regulation of arterial diameter and wall [Ca2+] in cerebral arteries of rat by membrane potential and intravascular pressure. The Journal of Physiology. 1998. 508; pp. 199-209.
Kok, Lai Chow et al. Effect of Heating on Pulmonary Veins: How to Avoid Pulmonary Vein Stenosis. Journal of Cardiovascular Electrophysiology. vol. 14, No. 3, Mar. 2003. pp. 250-254.
Kok, R. J. et al., Specific Delivery of Captopril to the Kidney with the Prodrug Captopril-Lysozyme, Aug. 16, 1998, Journal of Pharmacology and Experimental Therapeutics, vol. 288, No. 1, 1999 by The American Society for Pharmacology and Experimental Therapeutics, pp. 281-285.
Kon, V. Neural Control of Renal Circulation, Miner Electrolyte Metab. 1989;15:33-43.
Koomans, H.A., et al., Sympathetic hyperactivity in chronic renal failure: a wake-up call. J Am Soc Nephrol. 2004;15:524-37.
Kopp, U. et al., Dietary sodium loading increases arterial pressure in afferent renal-denervated rats, Hypertension, 2003, 42:968-973.
Kopp, U.C. et al., Renal sympathetic nerve activity modulates afferent renal nerve activity by PGE2-dependent activation of alpha1- and alpha2-adrenoceptors on renal sensory nerve fibers. Am J Physiol Regul Integr Comp Physiol. 2007;293:R1561-72.
Koyama, Shozo et al., Relative Contribution of Renal Nerve and Adrenal Gland to Renal Vascular Tone During Prolonged Canine Hemorrhagic Hypotension, Sep. 24, 1992, Circulatory Shock 1993, vol. 39, Wiley-Liss, Inc. 1993, pp. 269-274.
Kozak, Lola Jean, Ph.D et al., National Hospital Discharge Survey: 2001 Annual Summary with Detailed Diagnosis and Procedure Data, Vital and Health Statistics, Serices 13 No. 156, Jun. 2004, CDC, 206 pages.
Kumagai, K. et al. New Approach to Pulmonary Vein Isolation for Atrial Fibrillation Using a Multielectrode Basket Catheter. Circulation Journal. 2006;70:88-93.
Lafayette, Richard A., M.D., How Does Knocking Out Angiotensin II Activity Reduce Renal Injury in Mice?, Jun. 14, 1999, Journal Club, American Journal of Kidney Diseases, vol. 35, No. 1, Jan. 2000, National Kidney Foundation, Inc. 2000, pp. 166-172.
Lavie, Peretz, Ph.D. and Victor Hoffstein, M.D., Sleep Apnea Syndrome: A Possible Contributing Factor to Resistant Hypertension, Jun. 2001, Sleep 2001, vol. 24, No. 6, pp. 721-725.
Le Noble, J.L. et al., Pharmacological evidence for rapid destruction of efferent renal nerves in rats by intrarenal infusion of 6-hydroxydopamine. J Hypertens Suppl. 1985;3:S137-40.
Lee, Michael A. (editor). SPORTSMed. Connecticut State Medical Society Committee on the Medical Aspects of Sports. Fall/Winter 2005. 10 pgs.
Lee, Raphael C. et al., Biophysical Injury Mechanisms in Electronic Shock Trauma, Annu. Rev. Biomed. Eng., 2000, vol. 2, Copyright © 2000 by Annual Reviews, pp. 477-509.
Lee, Raphael C. et al., Clinical Sequelae Manifested in Electrical Shock Survivors, Presentation by the Electrical Trauma Research Program, The University of Chicago, 37 pages Dec. 24, 2004.
Lee, Raphael C. et al., Membrane Biology and Biophysics, Chapter 25, Surgical Research, 2001 Academic Press, pp. 297-305.
Lee, Raphael C., M.D., Sc.D. and Michael S. Kolodney, S.B., Electrical Injury Mechanisms: Electrical Breakdown of Cell Membranes, Oct. 1, 1986, Plastic and Reconstructive Surgery, Nov. 1987, vol. 80, No. 5, pp. 672-679.
Lenoble, L.M. et al., Selective efferent chemical sympathectomy of rat kidneys. Am J Physiol. 1985;249:R496-501.
Ligtenberg, Gerry M.D. et al., Reduction of Sympathetic Hyperactivity by Enalapril in Patients with Chronic Renal Failure, Apr. 29, 1999, New England Journal of Medicine 1999, vol. 340, No. 17, 1999 Massachusetts Medical Society, pp. 1321-1328.
Lin, Vernon W. H. et al., High intensity magnetic stimulation over the lumbosacral spine evokes antinociception in rats, Apr. 16, 2002, Clinical Neurophysiology, vol. 113, 2002 Elsevier Science Ireland Ltd., pp. 1006-1012.
Lipfert, Peter, M.D. et al., Tachyphylaxis to Local Anesthetics Does Not Result form Reduced Drug Effectiveness at the Nerve Itself, Aug. 3, 1988, Anesthesiology 1989, vol. 70, pp. 71-75.
Lohmeier, Thomas E. and Drew A. Hildebrandt, Renal Nerves Promote Sodium Excretion in Angiotensin-Induced Hypertension, Oct. 20, 1997, Hypertension 1998, vol. 31, part 2, 1998 American Heart Association, Inc., pp. 429-434.
Lohmeier, Thomas E. et al., Prolonged Activation of the Baroreflex Produces Sustained Hypotension, Harry Goldblatt Award, Nov. 26, 2003, Hypertension 2004, vol. 43, Part 2, 2004 American Heart Association, Inc., pp. 306-311.
Lohmeier, Thomas E. et al., Renal Nerves Promote Sodium Excretion During Long-Term Increases in Salt Intake, Oct. 23, 1998, Hypertension 1999, vol. 33, part II, 1999 American Heart Association, Inc., pp. 487-492.
Lohmeier, Thomas E. et al., Sustained influence of the renal nerves to attenuate sodium retention in angiotensin hypertension, Apr. 13, 2001, Am J Physiol Regulatory Integrative Comp Physiol, vol. 281, 2001 the American Physiological Society, pp. R434-R443.
Lohmeier, Thomas E., et al., Baroreflexes prevent neurally induced sodium retention in angiotensin hypertension, American Journal Physiol Regulatory Integrative Comp Physiol, vol. 279, 2000 the American Physiological Society, pp. R1437-R1448.
Lohmeier, Thomas E., Interactions Between Angiotensin II and Baroreflexes in Long-Term Regulation of Renal Sympathetic Nerve Activity, Circulation Research, Jun. 27, 2003, American Heart Association, Inc.2003, pp. 1282-1284.
Luff, S.E. et al., Two types of sympathetic axon innervating the juxtaglomerular arterioles of the rabbit and rat kidney differ structurally from those supplying other arteries, May 1, 1991, Journal of Neurocytology 1991, vol. 20, 1991 Chapman and Hall Ltd., pp. 781-795.
Luippold, G. et al., Chronic renal denervation prevents glomerular hyperfiltration in diabetic rats, Nephrol Dial Transplant (2004) 19:342-347.
Lundborg, C. et al., Clinical experience using intrathecal (IT) bupivacaine infusion in three patients with complex regional pain syndrome type I (CRPS-I), Acta Anaesthesiol Scand 1999, vol. 43, pp. 667-678.
Maeder, Micha, M.D. et al., Contrast Nephropathy: Review Focusing on Prevention, Jun. 22, 2004, Journal of the American College of

(56) **References Cited**

OTHER PUBLICATIONS

Cardiology Nov. 2, 2004, vol. 44, No. 9, 2004 by the American College of Cardiology Foundation, pp. 1763-1771.
Malpas, Simon C., What sets the long-term level of sympathetic nerve activity: is there a role for arterial baroreceptors?, Invited Review, Am J Physiol Regul lntegr Comp Physiol 2004, vol. 286, 2004 the American Physiological Society, pp. R1-R12.
Mancia, G., Grassi, G., Giannattasio, C., Seravalle, G., Sympathetic actrivation of pathogenesis of hypertension and progression of organ damage, Hypertension 1999, 34 (4 Pt 2): 724-728.
Marenzi, Giancarlo, M.D. et al., The Prevention of Radiocontrast-Agent-Induced Nephropathy by Hemofiltration, New England Journal of Medicine, Oct. 2, 2003, vol. 349 (14), 2003 Massachusetts Medical Society, pp. 1333-1340.
Market for infusion pumps grows with an aging population, NWL 97-01, The BBI Newsletter, vol. 20, No. 2, Feb. 1, 1997, American Health Consultants, Inc., pp. 6.
Martin, Jason B. et al., Gene Transfer to Intact Mesenteric Arteries by Electroporation, Mar. 27, 2000, Journal of Vascular Research 2000, vol. 37, 2000 S. Karger AG, Basel, pp. 372-380.
McCreery, Douglas B. et al., Charge Density and Charge Per Phase as Cofactors in Neural Injury Induced by Electrical Stimulation, IEEE Transactions on Biomedical Engineering, vol. 17, No. 10, Oct. 1990, pp. 996-1000.
McCullough, Peter A., M.D., MPH et al., Acute Renal Failure after Coronary Intervention: Incidence, Risk Factors and Relationship to Mortality, Apr. 14, 1997, AM J Med. 1997, vol. 103, 1997 Excerpta Medica, Inc., pp. 368-375.
McMurray, John J.V., M.D. and Eileen O'Meara, M.D., Treatment of Heart Failure with Spironolactone—Trial and Tribulations, Aug. 5, 2004, New England Journal of Medicine, vol. 351, No. 6, 2004 Massachusetts Medical Society, pp. 526-528.
Mcrobbie, D. and M.A. Foster, Thresholds for biological effects of time-varying magnetic fields, Dec. 16, 1983, Clin. Phys. Physiol. Meas. 1984, vol. 5, No. 2, 1984 The Institute of Physics, pp. 67-78.
Medtronic Neurostimulation Systems, Expanding the Array of Pain Control Solutions, informational pamphlet, 1999 Medtronic, Inc., 6 pages.
Medtronic, Spinal Cord Stimulation, Patient Management Guidelines for Clinicians, Medtronic, Inc. 1999, 115 pages.
Medtronic, SynchroMed Infusion System—Clinical Reference Guide for Pain Therapy, Medtronic, Inc. 1998, 198 pages.
Mehran, Roxana, Renal insufficiency and contrast nephropathy: The most common, least understood risk factor, Cardiovascular Research Foundation, Columbia University Medical Center, 2005, 86 slides.
Mess, Sarah a., M.D. et al., Implantable Baclofen Pump as an Adjuvant in Treatment of Pressure Sores, Mar. 1, 2003, Annals of Plastic Surgery, vol. 51, No. 5, Nov. 2003, Lippincott Williams & Wilkins 2003, pp. 465-467.
Micro ETS Hyperhidrosis USA Hyperhidrosis USA. 2 pgs. <URL: http://www.hyperhidrosis-usa.com/Index.html>. Nov. 6, 2006.
Mihran, Richard T. et al., Temporally-Specific Modification of Myelinated Axon Excitability in Vitro Following a Single Ultrasound Pulse, Sep. 25, 1989, Ultrasound in Med. & Biol. 1990, vol. 16, No. 3, pp. 297-309.
Miklavčič, D. et al, A Validated Model of in Vivo Electric Field Distribution in Tissues for Electrochemotherapy and for DNA Electrotransfer for Gene Therapy, Biochimica et Biophysica Acta, 1523, 2000, pp. 73-83, <http:www.elsevier.com/locate/bba>.
Mitchell, G. A. G., The Nerve Supply of the Kidneys, Aug. 20, 1949, Acta Anatomica, vol. X, Fasc. ½, 1950, pp. 1-37.
Morrisey, D.M. et al., Sympathectomy in the treatment of hypertension: Review of 122 cases, Lancet. 1953;1:403-408.
Moss, Nicholas G., Renal function and renal afferent and efferent nerve activity, Am. J. Physiol. 1982, vol. 243, 1982 the American Physiological Society, pp. F425-F433.
Munglani, Rajesh, The longer term effect of pulsed radiofrequency for neuropathic pain, Jun. 8, 1998, Pain 80, 1999, International Association for the Study of Pain 1999, Published by Elsevier Science B.V., pp. 437-439.
Naropin (ropivacaine HCl) Injection, RX only Description, AstraZeneca 2001, 3 pages.
National High Blood Pressure Education Program, 1995 Update of the Working Group Reports on Chronic Renal Failure and Renovascular Hypertension, presentation, 13 pages.
National Kidney Foundation, Are You at Increased Risk for Chronic Kidney Disease?, 2002 National Kidney Foundation, Inc., 14 pages.
Nelson, L. et al., Neurogenic Control of Renal Function in Response to Graded Nonhypotensive Hemorrhage in Conscious Dogs, Sep. 13, 1992, Am J. Physiol. 264, 1993, American Physiological Society 1993, pp. R661-R667.
Nikolsky, Eugenia, M.D. et al., Radiocontrast Nephropathy: Identifying the High-Risk Patient and the Implications of Exacerbating Renal Function, Rev Cardiovasc Med. 2003, vol. 4, Supp. 1, 2003 MedReviews, LLC, pp. S7-S14.
Non-Final Office Action; U.S. Appl. No. 10/408,665; Mailed on Mar. 21, 2006, 14 pgs.
Non-Final Office Action; U.S. Appl. No. 11/129,765; Mailed on May 18, 2007, 10 pgs.
Non-Final Office Action; U.S. Appl. No. 11/129,765; Mailed on Sep. 10, 2007, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/129,765; Mailed on Oct. 6, 2006, 30 pgs.
Non-Final Office Action; U.S. Appl. No. 11/133,925; Mailed on Oct. 8, 2008, 41 pgs.
Non-Final Office Action; U.S. Appl. No. 11/144,173; Mailed on Apr. 5, 2007, 33 pgs.
Non-Final Office Action; U.S. Appl. No. 11/144,173; Mailed on Sep. 10, 2007, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/144,298; Mailed Oct. 29, 2009, 8 pgs.
Non-Final Office Action; U.S. Appl. No. 11/144,298; Mailed on Apr. 5, 2007, 33 pgs.
Non-Final Office Action; U.S. Appl. No. 11/144,298; Mailed on Sep. 10, 2007, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/144,298; Mailed on Dec. 29, 2008, 7 pgs.
Non-Final Office Action; U.S. Appl. No. 11/145,122; Mailed on Apr. 11, 2007, 33 pgs.
Non-Final Office Action; U.S. Appl. No. 11/145,122; Mailed on Sep. 10, 2007, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/189,563; Mailed on May 28, 2009, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/233,814; Mailed on Jun. 17, 2008, 12 pgs.
Non-Final Office Action; U.S. Appl. No. 11/252,462; Mailed on Feb. 22, 2010, 6 pgs.
Non-Final Office Action; U.S. Appl. No. 11/266,993; Mailed on Jul. 8, 2009, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/266,993; Mailed on Dec. 30, 2008, 7 pgs.
Non-Final Office Action; U.S. Appl. No. 11/363,867; Mailed on Sep. 25, 2008, 10 pgs.
Non-Final Office Action; U.S. Appl. No. 11/368,553; Mailed on May 18, 2010, 4 pgs.
Non-Final Office Action; U.S. Appl. No. 11/368,553; Mailed on Oct. 7, 2009, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/368,809; Mailed on Dec. 3, 2009, 4 pgs.
Non-Final Office Action; U.S. Appl. No. 11/368,949; Mailed on Jun. 11, 2010, 6 pgs.
Non-Final Office Action; U.S. Appl. No. 11/368,971; Mailed on Aug. 24, 2010, 9 pgs.
Non-Final Office Action; U.S. Appl. No. 11/451,728; Mailed on Jun. 12, 2008, 41 pgs.
Non-Final Office Action; U.S. Appl. No. 11/451,728; Mailed on Jul. 2, 2009, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/451,728; Mailed on Dec. 28, 2009, 7 pgs.
Non-Final Office Action; U.S. Appl. No. 11/504,117; Mailed on Mar. 31, 2009, 10 pgs.
Non-Final Office Action; U.S. Appl. No. 11/599,649; Mailed on Mar. 30, 2009, 10 pgs.

(56) **References Cited**

OTHER PUBLICATIONS

Non-Final Office Action; U.S. Appl. No. 11/599,649; Mailed on Jun. 23, 2008, 9 pgs.
Non-Final Office Action; U.S. Appl. No. 11/599,723; Mailed on Jun. 26, 2009, 17 pgs.
Non-Final Office Action; U.S. Appl. No. 11/599,723; Mailed on Oct. 15, 2010, 16 pgs.
Non-Final Office Action; U.S. Appl. No. 11/599,882; Mailed on Jul. 6, 2009, 13 pgs.
Non-Final Office Action; U.S. Appl. No. 11/688,178; Mailed on Jun. 28, 2010, 5 pgs.
Non-Final Office Action; U.S. Appl. No. 11/840,142; Mailed on Apr. 3, 2009, 13 pgs.
Non-Final Office Action; U.S. Appl. No. 12/567,521; Mailed on Sep. 3, 2010, 9 pgs.
Non-Final Office Action; U.S. Appl. No. 12/616,708; Mailed Sep. 16, 2010, 10 pgs.
Non-Final Office Action; U.S. Appl. No. 12/725,375; Mailed on Oct. 12, 2010, 14 pgs.
Nozawa, T.et al., Effects of Long Term Renal Sympathetic Denervation on Heart Failure After Myocardial Infarction in Rats, Sep. 22, 2001, Heart Vessels, 2002, 16, Springer-Verlag 2002, pp. 51-56.
O'Hagan, K.P. et al., Renal denervation decreases blood pressure in DOCA-treated miniature swine with established hypertension, Am J Hypertens., 1990, 3:62-64.
Onesti, G. et al., Blood pressure regulation in end-stage renal disease and anephric man, Circ Res Suppl., 1975, 36 & 37: 145-152.
Osborn, et al., Effect of renal nerve stimulation on renal blood flow autoregulation and antinatriuresis during reductions in renal perfusion pressure, in Proceedings of the Society for Experimental Biology and Medicine, vol. 168, 77-81, 1981. (Abstract).
Packer, Douglas L. et al., Clinical Presentation, Investigation, and Management of Pulmonary Vein Stenosis Complication Ablation for Atrial Fibrillation, Circulation: Journal of the American Heart Association. Feb. 8, 2005, pp. 546-554.
Page, I.H. et al., The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension. J Clin Invest. 1935;14:27-30.
Page, I.H., et al., The Effect of Renal Efficiencyof Lowering Arterial Blood Pressure in Cases of Essential Nephritis, Hospital of the Rockefeller Institue, Jul. 12, 1934, 7 pgs.
Palmer, Biff, F., M.D., Managing Hyperkalemia Caused by Inhibitors of the Renin-Angiotensin-Aldosterone System, Aug. 5, 2004, The New England Journal of Medicine 2004, vol. 351;6, 2004 Massachusetts Medical Society, pp. 585-592.
Pappone, Carlo et al., [2005][P2-70] Safety Report of Circumferential Pulmonary Vein Ablation. A 9-Year Single-Center Experience on 6,442 Patients with Atrial Fibrillation, Abstract only. 1 page, May 2005.
Pappone, Carlo et al., [2004][759] Pulmonary Vein Denervation Benefits Paroxysmal Atrial Fibrillation Patients after Circumferential Ablation, Abstract only. 1 page, Jan. 5, 2004.
Pappone, Carol and Santinelli, Vincenzo. Multielectrode basket catheter: A new tool for curing atrial fibrillation? Heart Rhythm, vol. 3, Issue 4, pp. 385-386. Apr. 2006.
Peacock, J.M. and R. Orchardson, Action potential conduction block of nerves in vitro by potassium citrate, potassium tartrate and potassium oxalate, May 6, 1998, Journal of Clinical Periodontology, Munksgaard 1999, vol. 26, pp. 33-37.
Petersson, M. et al., Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. Eur Heart J. 2005;26:906-13.
Pettersson, A. et al., Renal interaction between sympathetic activity and ANP in rats with chronic ischaemic heart failure, Nov. 25, 1988, Acta Physiol Scand 1989, 135, pp. 487-492.
PHCL 762 Pharmacology of the Autonomic Nervous System, Chapter 2 and 6.8 in Mosby, http://www.kumc.edu/research/medicine/pharmacology/CAI/phcl762.html, last accessed Aug. 24, 2004, 14 pgs.
Pitt, B. et al., Effects of Eplerenone, Enalapril, and Eplerenone/Enalapril in Patients With Essential Hypertension and Left Ventricular Hypertrophy: The 4E-Left Ventricular Hypertrophy Study, Circulation, 2003, vol. 108, pp. 1831-1838.
Pliquett, U., Joule heating during solid tissue electroporation, Oct. 22, 2002, Med. Biol. Eng. Comput., 2003, vol. 41, pp. 215-219.
Podhajsky R.J. et al, The Histologic Effects of Pulsed and Continuous Radiofrequency Lesions at 42 C to Rat Dorsal Root Ganglion and Sciatic Nerve, Spine, vol. 30, No. 9, 2005, Lippincott Williams & Wilkins Inc., pp. 1008-1013.
Pope, Jill. Fixing a Hole: Treating Injury by Repairing Cells. The New York Academy of Sciences. Jul. 6, 2006. 6 pgs.
Popovic, Jennifer R. and Margaret J. Hall, 1999 National Hospital Discharge Survey, Apr. 24, 2001, Advance Data, No. 319, CDC, pp. 1-17 & 20.
Practice Guidelines Writing Committee and ESH/ESC Hypertension Guidelines Committee, Practice Guidelines for Primary Care Physicians: 2003 ESH/ESC Hypertension Guidelines, Published in Journal of Hypertension 2003, vol. 21, No. 10: 1011-1053, European Society of Hypertension 2003, pp. 1779-1786.
Programmable Infusion System, Pumps and Pump Selection, Medtronic Pain Therapies, Medtronic, Inc. Sep. 5, 2001, 2 pgs.
Pucihar, Gorazd et al., The influence of medium conductivity on electropermeabilization and survival of cells in vitro, May 31, 2001, Bioelectrochemistry, vol. 54, 2001, Elsevier Science B.V. 2001, pp. 107-115.
Pulmonary Concepts in Critical Care Breath Sounds, http://rnbob.tripod.com/breath.htm, last accessed Aug. 23, 2004, 5 pages.
Pulmonary Function Testing, http://jan.ucc.nau.edu/~daa/lecture/pft.htm, last accessed Aug. 23, 2004, 8 pages.
Purerfellner, Helmut and Martinek, Martin. Pulmonary vein stenosis following catheter ablation of atrial fibrillation. Current Opinion in Cardiology. 20; pp. 484-490. 2005.
Purerfellner, Helmut et al., Pulmonary Vein Stenosis by Ostial Irrigated-Tip Ablation: Incidence, Time Course, and Prediction, Journal of Cardiovascular Electrophysiology. vol. 14, No. 2, Feb. 2003. pp. 158-164.
Raji, A. R. M. And R. E. M. Bowden, Effects of High-Peak Pulsed Electromagnetic Field on the Degeneration and Regeneration of the Common Peroneal Nerve in Rats, The Journal of Bone and Joint Surgery Aug. 1983, vol. 65-B, No. 4, 1983 British Editorial Society of Bone and Joint Surgery, pp. 478-492.
Ram, C. Venkata S., M.D., Understanding refractory hypertension, May 15, 2004, Patient Care May 2004, vol. 38, pp. 12-16, 7 pages from http://www.patientcareonline.com/patcare/content/printContentPopup.jsp?id=108324.
Ravalia, A. et al., Tachyphylaxis and epidural anaesthesia, Edgware General Hospital, Correspondence, p. 529, Jun. 1989.
Renal Parenchymal Disease, Ch. 26, 5th Edition Heart Disease, A Textbook of Cardiovascular Medicine vol. 2, Edited by Eugene Braunwald, WB Saunders Company, pp. 824-825 1997.
Ribstein, Jean and Michael H. Humphreys, Renal nerves and cation excretion after acute reduction in functioning renal mass in the rat, Sep. 22, 1983, Am. J. Physiol., vol. 246, 1984 the American Physiological Society, pp. F260-F265.
Richebe, Philippe, M.D. et al., Immediate Early Genes after Pulsed Radiofrequency Treatment: Neurobiology in Need of Clinical Trials, Oct. 13, 2004, Anesthesiology Jan. 2005, vol. 102, No. 1, 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc., pp. 1-3.
Rihal, Charanjit S. et al., Incidence and Prognostic Importance of Acute Renal Failure After Percutaneous Coronary Intervention, Mar. 6, 2002, Circulation May 14, 2002, vol. 10, 2002 American Heart Association, Inc., pp. 2259-2264.
Rosen, S.M. et al., Relationship of Vascular Reactivity to Plasma Renin Concentration in Patients with Terminal Renal Failure, Proc. Dialysis Transplant Forum 1974, pp. 45-47.
Roth, Bradley J. and Peter J. Basser, A Model of the Stimulation of a Nerve Fiber by Electromagnetic Induction, IEEE Transactions on Biomedical Engineering, vol. 37, No. 6, Jun. 1990, pp. 588-597.
Rudin, Asa, M.D. et al., Postoperative Epidural or Intravenous Analgesia after Major Abdominal or Thoraco-Abdominal Surgery, The

(56) **References Cited**

OTHER PUBLICATIONS

Journal of the American Society of Anesthesiologists, Inc., Anesthesiology 2001, vol. 95, A-970, 1 page.
Rudnick, Michael R. et al., Contrast-induced nephropathy: How it develops, how to prevent it, Cleveland Clinic Journal of Medicine Jan. 2006, vol. 73, No. 1, pp. 75-87.
Rump, L.C., The Role of Sympathetic Nervous Activity in Chronic Renal Failure, J Clinical Basic Cardiology 2001, vol. 4, pp. 179-182.
Ruohonen, Jarmo et al., Modeling Peripheral Nerve Stimulation Using Magnetic Fields, Journal of the Peripheral Nervous System, vol. 2, No. 1, 1997, Woodland Publications 1997, pp. 17-29.
Saad, Eduardo B. et al., Pulmonary Vein Stenosis After Radiofrequency Ablation of Atrial Fibrillation: Functional Characterization, Evolution, and Influence of the Ablation Strategy, Circulation. 108; pp. 3102-3107. 2003.
Sabbah, Hani N., Animal Models for Heart Failure and Device Development, Henry Ford Health System. 24 slides, Oct. 17, 2005.
Schauerte, P et al., Focal atrial fibrillation: experimental evidence for a pathophysiologic role of the autonomic nervous system, Journal of Cardiovascular Electrophysiology. 12(5). May 2001. Abstract only. 2 pgs.
Schauerte, P et al., Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation, Circulation. 102(22). Nov. 28, 2000. Abstract only. 2 pgs.
Schauerte, P. et al., Transvenous parasympathetic nerve stimulation in the inferior vena cava and atrioventricular conduction, Journal of Cardiovascular Electrophysiology. 11(1). Jan. 2000. Abstract only. 2 pgs.
Scheiner, Avram, Ph.D., The design, development and implementation of electrodes used for functional electrial stimulation, Thesis paper, Case Western Reserve University, May 1992, 220 pages.
Scherlag, BJ and Po, S., The intrinsic cardiac nervous system and atrial fibrillation, Current Opinion in Cardiology. 21(1):51-54, Jan. 2006. Abstract only. 2 pgs.
Schlaich, M.P. et al., Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. Circulation. 2003;108:560-5.
Schlaich, M.P. et al., Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation, Hypertension, 2004, 43:169-175.
Schmitt, Joseph et al., Intravascular Optical Coherence Tomography—Opening a Window into Coronary Artery Disease, LightLab Imaging, Inc. Business Briefing: European Cardiology 2005.
Schoenbach, Karl H. et al, Intracellular Effect of Ultrashort Electrical Pulses, Dec. 26, 2000, Bioelectromagnetics, vol. 22, 2001, Wiley-Liss, Inc. 2001, pp. 440-448.
Schrier, Robert et al., Cardiac and Renal Effects of Standard Versus Rigorous Blood Pressure Control in Autosomal-Dominant Polycistic Kidney Disease, Mar. 23, 2002, Journal of the American Society of Nephrology, American Society of Nephrology 2002, pp. 1733-1739.
Scremin, Oscar U., M.D., Ph.D. and Daniel P. Holschneider, M.D., 31 & 32.. An Implantable Bolus Infusion Pump for the Neurosciences, FRP, Apr. 2005, 3 pages.
Sensorcaine—MPF Spinal Injection, informational document, AstraZeneca 2001, 2 pgs.
Shah, D.C., Haissaguerre, M., Jais, P., Catheter ablation of pulmonary vein foci for atrial fibrillation: pulmonary vein foci ablation for atrial firbrillation, Thorac Cardiovasc Surg, 1999, 47 (suppl. 3): 352-356.
Shannon, J.L. et al., Studies on the innervation of human renal allografts, J Pathol. 1998, vol. 186, pp. 109-115.
Shlipak, M.G. et al., The clinical challenge of cardiorenal syndrome. Circulation. 2004;1 10:1514-7.
Shupak, Naomi M., Therapeutic Uses of Pulsed Magnetic-Field Exposure: A Review, Radio Science Bulletin Dec. 2003, No. 307, pp. 9-32.
Shu-Qing, Liu et al., Old spinal cord injury treated by pulsed electric stimulation, General Hospital of Beijing Command, Beijing, Dec. 6, 1990, 5 pages. (full article in Chinese; abstract on last page).
Siegel, RJ et al., Clinical demonstration that catheter-delivered ultrasound energy reverses arterial vasoconstriction, Journal of the American College of Cardiology. 1992. 20; 732-735. Summary only. 2 pgs.
Simpson, B. et al., Implantable spinal infusion devices for chronic pain and spasticity: an accelerated systematic review, ASERNIP-S Report No. 42, Adelaide, South Australia, ASERNIP-S, May 2003, 56 pages.
Sisken, B.F. et al., 229.17 Influence of Non-Thermal Pulsed Radiofrequency Fields (PRF) on Neurite Outgrowth, Society for Neuroscience, vol. 21, 1995, 2 pages.
Skeie, B. et al., Effect of chronic bupivacaine infusion on seizure threshold to bupivacaine, Dec. 28, 1986, Acta Anaesthesiol Scand 1987, vol. 31, pp. 423-425.
Skopec, M., A Primer on Medical Device Interactions with Magnetic Resonance Imaging Systems, Feb. 4, 1997, CDRH Magnetic Resonance Working Group, U.S. Department of Heatlh and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Updated May 23, 1997, 17 pages, http://www.fda.gov/cdrh/ode/primerf6.html, (last accessed Jan. 23, 2006.
Slappendel, Robert et al., The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study, Jun. 26, 1997, Pain 73, 1997 International Association for the Study of Pain, Elsevier Science B.V., pp. 159-163.
Sluijter, M.D., Ph.D., Pulsed Radiofrequency, May 17, 2005, Anesthesiology Dec. 2005, vol. 103, No. 6, 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc., pp. 1313-1314.
Sluijter, M.D., Ph.D., Radiofrequency Part 1: The Lumbosacral Region, Chapter 1 Mechanisms of Chronic Pain and part of Chapter 2 Spinal Pain, 2001 FlivoPress SA, Meggen (LU), Switzerland, pp. 1-26.
Sluijter, M.D., Ph.D., Radiofrequency Part 2: Thoracic and Cervical Region, Headache and Facial Pain, various pages from, FlivoPress SA, Meggen (LU), Switzerland, 13 pages 2002.
Sluijter, M.D., Ph.D., The Role of Radiofrequency in Failed Back Surgery Patients, Current Review of Pain 2000, vol. 4, 2000 by Current Science Inc., pp. 49-53.
Smithwick, R.H. et al., Hypertension and associated cardiovascular disease: comparison of male and female mortality rates and their influence on selection of therapy, JAMA, 1956, 160:1023-1033.
Smithwick, R.H. et al., Splanchnicectomy for essential hypertension, Journal Am Med Assn, 1953;152:1501-1504.
Smithwick, R.H., Surgical treatment of hypertension, Am J Med 1948, 4:744-759.
Sobotka, Paul A., Treatment Strategies for Fluid Overload, CHF Patients, CHF Solutions. Transcatheter Cardiovascular Therapeutics 2005. 20 slides.
Solis-Herruzo, J.A. et al., Effects of lumbar sympathetic block on kidney function in cirrhotic patients with hepatorenal syndrome, Journal of Hepatology, 1987; 5: 167-173.
Souza, D.R.B. et al., Chronic experimental myocardial infarction produces antinatriuresis by a renal nerve-dependent mechanism, Oct. 14, 2003, Brazilian Journal of Medical and Biological Research 2004, vol. 37, pp. 285-293.
Standl, Thomas, M.D., et al., Patient-controlled epidural analgesia reduces analgesic requirements compared to continuous epidural infusion after major abdominal surgery, Aug. 29, 2002, Canada Journal of Anesthesia 2003, vol. 50 (3), pp. 258-264.
Steffen, W. et al., Catheter-delivered high intensity, low frequency ultrasound induces vasodilation in vivo, European Heart Journal. 1994. 15; pp. 369-376.
Steg, PG et al., Pulsed ultraviolet laser irradiation produces endothelium-independent relaxation of vascular smooth muscle, Circulation: Journal of the American Heart Association. 1989. pp. 189-197.
Stone, Gregg W., M.D. et al., Fenoldopam Mesylate for the Prevention of Contrast-Induced Nephropathy, JAMA Nov. 5, 2003, vol. 290, No. 17, 2003 American Medical Association, pp. 2284-2291.
Strojek, K. et al., Lowering of microalbuminuria in diabetic patients by a sympathicoplegic agent: novel approach to prevent progression of diabetic nephropathy? J Am Soc Nephrol. 2001;12:602-5.

(56) **References Cited**

OTHER PUBLICATIONS

Summary, Critical Reviews in Biomedical Engineering, vol. 17, Issue 5, 1989, pp. 515-529.
Sung, Duk Hyun, M.D. et al., Phenol Block of Peripheral Nerve Conduction: Titrating for Optimum Effect, Jun. 27, 2000, Arch. Phys. Med. Rehabil. vol. 82, May 2001, pp. 671-676.
Taka, Tomomi et al., Impaired Flow-Mediated Vasodilation in vivo and Reduced Shear-Induced Platelet Reactivity in vitro in Response to Nitric Oxide in Prothrombotic, Stroke-Prone Spontaneously Hypertensive Rats, Pathophysiology of Haemostasis and Thrombosis. Dec. 23, 2002. pp. 184-189.
Taler, Sandra J. et al., Resistant Hypertension, Comparing Hemodynamic Management to Specialist Care, Mar. 12, 2002, Hypertension 2002, vol. 39, 2002 American Heart Association, Inc., pp. 982-988.
Tamborero, David et al., Incidence of Pulmonary Vein Stenosis in Patients Submitted to Atrial Fibrillation Ablation: A Comparison of the Selective Segmental Ostial Ablation vs. the Circumferential Pulmonary Veins Ablation, Journal of Intervocational Cardiac Electrophysiology. 14; pp. 41-25. 2005.
Tay, Victoria KM, et al., Computed tomography fluoroscopy-guided chemical lumbar sympathectomy: Simple, safe and effective, Oct. 31, 2001, Diagnostic Radiology, Australasian Radiology 2002, vol. 46, pp. 163-166.
Terashima, Mitsuyasu et al. Feasibility and Safety of a Novel CryoPlasty™ System. Poster. 1 page, Mar. 15, 2002.
Thatipelli et al., CT Angiography of Renal Artery Anatomy for Evaluating Embolic Protection Devices, Journal of Vascular and Interventional Radiology, Jul. 2007, pp. 842-846.
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ALLHAT Research Group, JAMA, 2002, vol. 288, pp. 2981-2997.
Thomas, John R. and Oakley, E. Howard N. Chapter 15: Nonfreezing Cold Injury Medical Aspects of Harsh Environments, vol. 1. pp. 467-490, 2001.
Thompson, Gregory W., et al., Bradycardia Induced by Intravascular Versus Direct Stimulation of the Vagus Nerve, Aug. 24, 1997, The Society of Thoracic Surgeons 1998, pp. 637-642.
Thrasher, Terry N., Unloading arterial baroreceptors causes neurogenic hypertension, Dec. 4, 2001, Am J. Physiol Regulatory Integrative Comp Physiol, vol. 282, 2002 the American Physiological Society, pp. R1044-R1053.
Tokuno, Hajime A. et al., Local anesthetic effects of cocaethylene and isopropylcocaine on rat peripheral nerves, Oct. 7, 2003, Brain Research 996, 2004, Elsevier B.V. 2003, pp. 159-167.
Trapani, Angelo J. et al., Neurohumoral interactions in conscious dehydrated rabbit, Am. J. Physiol. 254, 1988, the American Physiological Society 1988, pp. R338-R347.
Trock, David H. et al., The Effect of Pulsed Electromagnetic Fields in the Treatment of Osteoarthritis of the Knee and Cervical Spine. Report of Randomized, Double Blind, Placebo Controlled Trials, Mar. 22, 1994, The Journal of Rheumatology 1994, vol. 21, pp. 1903-1911.
Troiano, Gregory C. et al., The Reduction in Electroporation Voltages by the Addition of a Surfactant to Planar Lipid Bilayers, May 12, 1998, Biophysical Journal, vol. 75, Aug. 1998, the Biophysical Society 1998, pp. 880-888.
Trumble, Dennis R. and James A. MaGovern, Comparison of Dog and Pig Models for Testing Substernal Cardiac Compression Devices, Nov. 2003, ASAIO Journal 2004, pp. 188-192.
Tsai, E., Intrathecal drug delivery for pain indications, technique, results, Pain Lecture presentation, Jun. 8, 2001, 31 pages.
Uematsu, Toshihiko, M.D., Ph.D., F.I.C.A. et al., Extrinsic Innervation of the Canine Superior Vena Cava, Pulmonary, Portal and Renal Veins, Angiology—Journal of Vascular Diseases, Aug. 1984, pp. 486-493.
United States Renal Data System, USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003, 593 pages.
Upadhyay, Pramod, Electroporation of the skin to deliver antigen by using a piezo ceramic gas igniter, Jan. 27, 2001, International Journal of Pharmaceutics, vol. 217, 2001 Elsevier Science B.V., pp. 249-253.
Valente, John F. et al., Laparoscopic renal denervation for intractable ADPKD-related pain, Aug. 24, 2000, Nephrol Dial Transplant 2001, vol. 16, European Renal Association—European Dialysis and Transplant Association, p. 160.
Van Antwerp, Bill and Poonam Gulati, Protein Delivery from Mechanical Devices Challenges and Opportunities, Medtronic presentation, 19 pages, Jul. 2003.
Velazquez, Eric J., An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry, Aug. 5, 2004, European Heart Journal vol. 25, 2004 Elsevier, pp. 1911-1919.
Velez-Roa, Sonia, M.D. et al., Peripheral Sympathetic Control During Dobutamine Infusion: Effects of Aging and Heart Failure, Jul. 7, 2003, Journal of the American College of Cardiology, vol. 42, No. 9, 2003, American College of Cardiology Foundation 2003, pp. 1605-1610.
Villarreal, Daniel et al., Effects of renal denervation on postprandial sodium excretion in experimental heart failure, Oct. 29, 1993, Am J Physiol 266, 1994, pp. R1599-R1604.
Villarreal, Daniel et al., Neurohumoral modulators and sodium balance in experimental heart failure, Nov. 6, 1992, Am. J. Physiol, vol. 264, 1993, pp. H1187-H1193.
Vonend, O. et al., Moxonidine treatment of hypertensive patients with advanced renal failure. J Hypertens. 2003;21:1709-17.
Wagner, C.D. et al., Very low frequency oscillations in arterial blood pressure after autonomic blockade in conscious dogs, Feb. 5, 1997, Am J Physiol Regul lntegr Comp Physiol 1997, vol. 272, 1997 the American Physiological Society, pp. 2034-2039.
Wald, Jan D., Ph.D, et al., Cardiology Update: 2003, Sep. 11, 2003, AG Edwards 2003, 120 pages.
Wang, Xi et al., Alterations of adenylyl cyclase and G proteins in aortocaval shunt-induced heart failure, Jul. 2004, AM J Physiol Heart Circ Physiol vol. 287, 2004 the American Physiological Society, pp. H118-H125.
Weaver, James C., Chapter 1 Electroporation Theory, Concepts and Mechanisms, Methods in Molecular Biology, vol. 55, Plant Cell Electroporation and Electrofusion Protocols, Edited by J.A. Nickoloff, Humana Press Inc., pp. 3-28, 1995.
Weaver, James C., Electroporation: A General Phenomenon for Manipulating Cells and Tissues, Oct. 22, 1992, Journal of Cellular Biochemistry, vol. 51, 1993 Wiley-Liss, Inc., pp. 426-435.
Weiner, Richard L., M.D., Peripheral nerve neurostimulation, Neurosurg. Clin. N. Am. vol. 14, 2003, Elsevier, Inc. 2003, pp. 401-408.
Weisbord, Steven D., M.D. and Paul M. Palevsky, M.D., Radiocontrast-Induced Acute Renal Failure, Jul. 10, 2004, Journal of Intensive Care Medicine 2005, vol. 20 (2), 2005 Sage Publications, pp. 63-75.
Whitelaw, G.P., Kinsey, D., Smithwick, R.H., Factors influencing the choice of treatment in essential hypertension: surgical, medical, or a combination of both, Am J Surg, 1964, 107:220-231.
Wilson, D.H. et al., The Effects of Pulsed Electromagnetic Energy on Peripheral Nerve Regeneration, Annals New York Academy of Sciences, Oct. 1974, pp. 575-585.
Wolinsky, Harvey, M.D. PhD and Swan N. Thung, M.D., Use of a Perforated Balloon Catheter to Deliver Concentrated Heparin Into the Wall of the Normal Canine Artery, Aug. 30, 1989, JACC 1990, vol. 15, 1990 by the American College of Cardiology, pp. 475-481.
Wyss, J. Michael et al., Neuronal control of the kidney: Contribution to hypertension, Apr. 8, 1991, Can. J. Physiol. Pharmacol. 1992;70: 759-770.
Yamaguchi, Jun-ichi, M.D. et al., Prognostic Significance of Serum Creatinine Concentration for In-Hospital Mortality in Patients with Acute Myocardial Infarction Who Underwent Successful Primary Percutaneous Coronary Intervention (from the Heart Institute of Japan Acute Myocardial Infarction [HIJAMI] Registry), Feb. 24, 2004, The American Journal of Cardiology vol. 93, Jun. 15, 2004, 2004 by Excerpta Medica, Inc., pp. 1526-1528.
Ye, Richard D., M.D., Ph.D., Pharmacology of the Peripheral Nervous System, E-425 MSB, 6 pages, Jan. 2000.

(56) **References Cited**

OTHER PUBLICATIONS

Ye, S. et al., A limited renal injury may cause a permanent form of neurogenic hypertension. Am J Hypertens. 1998;11:723-8.
Ye, Shaohua et al., Renal Injury Caused by Intrarenal Injection of Pheno Increases Afferent and Efferent Renal Sympathetic Nerve Activity, Mar. 12, 2002, American Journal of Hypertension, Aug. 2002, vol. 15, No. 8, 2002 the American Journal of Hypertension, Ltd. Published by Elsevier Science Inc., pp. 717-724.
Yong-Quan, Dong et al., The therapeutic effect of pulsed electric field on experimental spinal cord injury, Beijing Army General Hospital of People's Liberation Army, Beijing, 5 pages (full article in Chinese; abstract on last page) Mar. 30, 1992.
Young, James B., M.D., FACC, Management of Chronic Heart Failure: What Do Recent Clinical Trials Teach Us?, Reviews in Cardiovascular Medicine, vol. 5, Suppl. 1, 2004, MedReviews, LLC 2004, pp. S3-S9.
Yu, Wen-Chung et al. Acquired Pulmonary Vein Stenosis after Radiofrequency Catheter Ablation of Paroxysmal Atrial Fibrillation. Journal of Cardiovascular Electrophysiology. vol. 12, No. 8. Aug. 2001. pp. 887-892.
Zanchetti, A. et al., Neural Control of the Kidney—Are There Reno-Renal Reflexes?, Clin. And Exper. Hyper. Theory and Practice, A6 (1&2), 1984, Marcel Dekker, Inc. 1984, pp. 275-286.
Zanchetti, A. et al., Practice Guidelines for Primary Care Physicians: 2003 ESH/ESC Hypertension Guidelines, Journal of Hypertension, vol. 21, No. 10, 2003, pp. 1779-1786.
Zanchetti, A.S., Neural regulation of renin release: Experimental evidence and clinical implications in arterial hypertension, Circulation, 1977, 56(5) 691-698.
Zimmermann, Ulrich, Electrical Breakdown, Electropermeabilization and Electrofusion, Rev. Physiol. Biochem. Pharmacol., vol. 105, Springer-Verlag 1986, pp. 175-256.
Zoccali, C. et al., Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation. 2002;105:1354-9.
Zucker, Irving H. et al., The origin of sympathetic outflow in heart failure: the roles of angiotensin II and nitric oxide, Progress in Biophysics & Molecular Biology, vol. 84, 2004, Elsevier Ltd. 2003, pp. 217-232.
Zundert, Jan Van, M.D. Fipp and Alex Cahana, M.D. Daapm, Pulsed Radiofrequency in Chronic Pain Management: Looking for the Best Use of Electrical Current, Pain Practice 2005, vol. 5, Issue 2, 2005 World Institute of Pain, pp. 74-76.
Ahmed, Humera et al., Renal Sympathetic Denervation Using an Irrigated Radiofrequency Ablation Catheter for the Management of Drug-Resistant Hypertension, JACC Cardiovascular Interventions, vol. 5, No. 7, 2012, pp. 758-765.
Avitall et al., "The creation of linear contiguous lesions in the atria with an expandable loop catheter," Journal of the American College of Cardiology, 1999; 33; pp. 972-984.
Blessing, Erwin et al., Cardiac Ablation and Renal Denervation Systems Have Distinct Purposes and Different Technical Requirements, JACC Cardiovascular Interventions, vol. 6, No. 3, 2013, 1 page.
ClinicalTrials.gov, Renal Denervation in Patients with uncontrolled Hypertension in Chinese (2011), 6pages. www.clinicaltrials.gov/ct2/show/NCT01390831.
Excerpt of Operator's Manual of Boston Scientific's EPT-1000 XP Cardiac Ablation Controller & Accessories, Version of Apr. 2003, (6 pages).
Excerpt of Operator's Manual of Boston Scientific's Maestro 30000 Cardiac Ablation System, Version of Oct. 17, 2005 , (4 pages).
Schneider, Peter A., "Endovascular Skills—Guidewire and Catheter Skills for Endovascular Surgery," Second Edition Revised and Expanded, 10 pages, (2003).
Kandarpa, Krishna et al., "Handbook of Interventional Radiologic Procedures", Third Edition, pp. 194-210 (2002).
ThermoCool Irrigated Catheter and Integrated Ablation System, Biosense Webster (2006), 6 pages.
Mount Sinai School of Medicine clinical trial for Impact of Renal Sympathetic Denervation of Chronic Hypertension, Mar. 2013, 11 pages. http://clinicaltrials.gov/ct2/show/NCT01628198.
Opposition to European Patent No. EP1802370, Granted Jan. 5, 2011, Date of Opposition Oct. 5, 2011, 20 pages.
Opposition to European Patent No. EP2037840, Granted Dec. 7, 2011, Date of Opposition Sep. 7, 2012, 25 pages.
Opposition to European Patent No. EP2092957, Granted Jan. 5, 2011, Date of Opposition Oct. 5, 2011, 26 pages.
Oz, Mehmet, Pressure Relief, TIME, Jan. 9, 2012, 2 pages. <www.time.come/time/printout/0,8816,2103278,00.html>.
Prochnau, Dirk et al., Catheter-based renal denervation for drug-resistant hypertension by using a standard electrophysiology catheter; Euro Intervention 2012, vol. 7, pp. 1077-1080.
Papademetriou, Vasilios, Renal Sympathetic Denervation for the Treatment of Difficult-to-Control or Resistant Hypertension, Int. Journal of Hypertension, 2011, 8 pages.
Holmes et al., Pulmonary Vein Stenosis Complicating Ablation for Atrial Fibrillation: Clinical Spectrum and Interventional Considerations, JACC: Cardiovascular Interventions, 2: 4, 2009, 10 pages.
Purerfellner, Helmut et al., Incidence, Management, and Outcome in Significant Pulmonary Vein Stenosis Complicating Ablation for Atrial Fibrillation, Am. J. Cardiol , 93, Jun. 1, 2004, 4 pages.
Tsao, Hsuan-Ming, Evaluation of Pulmonary Vein Stenosis after Catheter Ablation of Atrial Fibrillation, Cardiac Electrophysiology Review, 6, 2002, 4 pages.
Wittkampf et al., "Control of radiofrequency lesion size by power regulation," Journal of the American Heart Associate, 1989, 80: pp. 962-968.
Zheng et al., "Comparison of the temperature profile and pathological effect at unipolar, bipolar and phased radiofrequency current configurations," Journal of Interventional Cardiac Electrophysiology, 2001, pp. 401-410.
U.S. Appl. No. 95/002,110, filed Aug. 29, 2012, Demarais et al.
U.S. Appl. No. 95/002,209, filed Sep. 13, 2012, Levin et al.
U.S. Appl. No. 95/002,233, filed Sep. 13, 2012, Levin et al.
U.S. Appl. No. 95/002,243, filed Sep. 13, 2012, Levin et al.
U.S. Appl. No. 95/002,253, filed Sep. 13, 2012, Demarais et al.
U.S. Appl. No. 95/002,255, filed Sep. 13, 2012, Demarais et al.
U.S. Appl. No. 95/002,292, filed Sep. 14, 2012, Demarais et al.
U.S. Appl. No. 95/002,327, filed Sep. 14, 2012, Demarais et al.
U.S. Appl. No. 95/002,335, filed Sep. 14, 2012, Demarais et al.
U.S. Appl. No. 95/002,336, filed Sep. 14, 2012, Levin et al.
U.S. Appl. No. 95/002,356, filed Sep. 14, 2012, Demarais et al.
"2011 Edison Award Winners." Edison Awards: Honoring Innovations & Innovators, 2011, 6 pages, attp://www.edisonawards.com/BestNewProduct_2011.php>.
"2012 top 10 advances in heart disease and stroke research: American Heart Association/America Stroke Association Top 10 Research Report." American Heart Association, Dec. 17, 2012, 5 pages, <http://newsroom.heart.org/news/2012-top-10-advances-in-heart-241901>.
"Ardian(R) Receives 2010 EuroPCR Innovation Award and Demonstrates Further Durability of Renal Denervation Treatment for Hypertension." PR Newswire, Jun. 3, 2010, 2 pages, <http://www.prnewswire.com/news-releases/ardianr-receives-2010-europcr-innovation-award-and-demonstrates-further-durability-of-renal-denervation-treatment-for-hypertension-95545014.html>.
"Boston Scientific to Acquire Vessix Vascular, Inc.: Company to Strengthen Hypertension Program with Acquisition of Renal Denervation Technology." Boston Scientific: Advancing science for life—Investor Relations, Nov. 8, 2012, 2 pages, <http://phx.corporate-ir.net/phoenix.zhtml?c=62272&p=irol-newsArticle&id=1756108>.
"Cleveland Clinic Unveils Top 10 Medical Innovations for 2012: Experts Predict Ten Emerging Technologies that will Shape Health Care Next Year." Cleveland Clinic, Oct. 6, 2011, 2 pages. <http://my.clevelandclinic.org/media_relations/library/2011/2011-10-6-cleveland-clinic-unveils-top-10-medical-innovations-for-2012.aspx>.
"Does renal denervation represent a new treatment option for resistant hypertension?" Interventional News, Aug. 3, 2010, 2 pages.

(56) **References Cited**

OTHER PUBLICATIONS

<http://www.cxvascular.com/in-latest-news/interventional-news---latest-news/does-renal-denervation-represent-a-new-treatment-option-for-resistant-hypertension>.
"Iberis—Renal Sympathetic Denervation System: Turning innovation into quality care." [Brochure], Terumo Europe N.V., 2013, Europe, 3 pages.
"Neurotech Reports Announces Winners of Gold Electrode Awards." Neurotech business report, 2009. 1 page <http://www.neurotechreports.com/pages/goldelectrodes09.html>.
"Quick. Consistent. Controlled. OneShot renal Denervation System" [Brochure], Covidien: positive results for life, 2013, (n.l.), 4 pages.
"Renal Denervation Technology of Vessix Vascular, Inc. been acquired by Boston Scientific Corporation (BSX) to pay up to $425 Million." Vessix Vascular Pharmaceutical Intelligence: A blog specializing in Pharmaceutical Intelligence and Analytics, Nov. 8, 2012, 21 pages, <http://pharmaceuticalintelligence.com/tag/vessix-vascular/>.
"The Edison Awards™" Edison Awards: Honoring Innovations & Innovators, 2013, 2 pages, <http://www.edisonawards.com/Awards.php>.
"The Future of Renal denervation for the Treatment of Resistant Hypertension." St. Jude Medical, Inc., 2012, 12 pages.
"Vessix Renal Denervation System: So Advanced Its Simple." [Brochure], Boston Scientific: Advancing science for life, 2013, 6 pages.
Asbell, Penny, "Conductive Keratoplasty for the Correction of Hyperopia." Tr Am Ophth Soc, 2001, vol. 99, 10 pages.
Badoer, Emilio, "Cardiac afferents play the dominant role in renal nerve inhibition elicited by volume expansion in the rabbit." Am J Physiol Regul Integr Comp Physiol, vol. 274, 1998, 7 pages.
Bengel, Frank, "Serial Assessment of Sympathetic Reinnervation After Orthotopic Heart Transplantation: A longitudinal Study Using PET and C-11 Hydroxyephedrine." Circulation, vol. 99, 1999,7 pages.
Benito, F., et al. "Radiofrequency catheter ablation of accessory pathways in infants." Heart, 78:160-162 (1997).
Bettmann, Michael, Carotid Stenting and Angioplasty: A Statement for Healthcare Professionals From the Councils on Cardiovascular Radiology, Stroke, Cardio-Thoracic and Vascular Surgery, Epidemiology and Prevention, and Clinical Cardiology, American Heart Association, Circulation, vol. 97, 1998, 4 pages.
Bohm, Michael et al., "Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry." EuroIntervention, vol. 9, 2013, 9 pages.
Brosky, John, "EuroPCR 2013: CE-approved devices line up for renal denervation approval." Medical Device Daily, May 28, 2013, 3 pp., <http://www.medicaldevicedaily.com/servlet/com.accumedia.web.Dispatcher?next=bioWorldHeadlines_article&forceid=83002>.
Davis, Mark et al., "Effectiveness of Renal Denervation Therapy for Resistant Hypertension." Journal of the American College of Cardiology, vol. 62, No. 3, 2013, 11 pages.
Dibona, G.F. "Sympathetic nervous system and kidney in hypertension." Nephrol and Hypertension, 11: 197-200 (2002).
Dubuc, M., et al., "Feasibility of cardiac cryoablation using a transvenous steerable electrode catheter." J Interv Cardiac Electrophysiol, 2:285-292 (1998).
Final Office Action; U.S. Appl. No. 12/827,700; Mailed on Feb. 5, 2013, 61 pages.
Geisler, Benjamin et al., "Cost-Effectiveness and Clinical Effectiveness of Catheter-Based Renal Denervation for Resistant Hypertension." Journal of the American College of Cardiology, Col. 60, No. 14, 2012, 7 pages.
Gelfand, M., et al., "Treatment of renal failure and hypertension." U.S. Appl. No. 60/442,970, Jan. 29, 2003, 23 pages.
Gertner, Jon, "Meet the Tech Duo That's Revitalizing the Medical Device Industry." Fast Company, Apr. 15, 2013, 6:00 AM, 17 pages, <http://www.fastcompany.com/3007845/meet-tech-duo-thats-revitalizing-medical-device-industry>.
Golwyn, D. H., Jr., et al. "Percutaneous Transcatheter Renal Ablation with Absolute Ethanol for Uncontrolled Hypertension or Nephrotic Syndrome: Results in 11 Patients with End-Stage Renal Disease." JVIR, 8: 527-533 (1997).
Hall, W. H., et al. "Combined embolization and percutaneous radiofrequency ablation of a solid renal tumor." *Am. J. Roentgenol*,174: 1592-1594 (2000).
Han, Y.-M, et al., "Renal artery ebolization with diluted hot contrast medium: An experimental study." J Vasc Interv Radiol, 12: 862-868 (2001).
Hansen, J. M., et al. "The transplanted human kidney does not achieve functional reinnervation." *Clin. Sci*, 87: 13-19 (1994).
Hendee, W. R. et al. "Use of Animals in Biomedical Research: The Challenge and Response." *American Medical Association White Paper* (1988) 39 pages.
Hering, Dagmara et al., "Chronic kidney disease: role of sympathetic nervous system activation and potential benefits of renal denervation." EuroIntervention, vol. 9, 2013, 9 pages.
Huang et al., "Renal denervation prevents and reverses hyperinsulinemia-induced hypertension in rats." Hypertension 32 (1998) pp. 249-254.
Imimdtanz, "Medtronic awarded industry's highest honour for renal denervation system." The official blog of Medtronic Australasia, Nov. 12, 2012, 2 pages, <http://97waterlooroad.wordpress.com/2012/11/12/medtronic-awarded-industrys-highest-honour-for-renal-denervation-system/>.
Kaiser, Chris, AHA Lists Year's Big Advances in CV Research, medpage Today, Dec. 18, 2012, 4 pages, <http://www.medpagetoday.com/Cardiology/PCI/36509>.
Kompanowska, E., et al., "Early Effects of renal denervation in the anaesthetised rat: Natriuresis and increased cortical blood flow." J Physiol, 531. 2:527-534 (2001).
Lee, S.J., et al. "Ultrasonic energy in endoscopic surgery." Yonsei Med J, 40:545-549 (1999).
Linz, Dominik et al., "Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs." Heart Rhythm, vol. 0, No. 0, 2013, 6 pages.
Lustgarten, D.L.,et al., "Cryothermal ablation: Mechanism of tissue injury and current experience in the treatment of tachyarrhythmias." Progr Cardiovasc Dis, 41:481-498 (1999).
Mabin, Tom et al., "First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension." EuroIntervention, vol. 8, 2012, 5 pages.
Mahfoud, Felix et al., "Ambulatory Blood Pressure Changes after Renal Sympathetic Denervation in Patients with Resistant Hypertension." Circulation, 2013, 25 pages.
Mahfoud, Felix et al., "Expert consensus document from the European Society of Cardiology on catheter-based renal denervation." European Heart Journal, 2013, 9 pages.
Mahfoud, Felix et al., "Renal Hemodynamics and Renal Function After Catheter-Based Renal Sympathetic Denervation in Patients With Resistant Hypertension." Hypertension, 2012, 6 pages.
Medical-Dictionary.com, Definition of "Animal Model," http://medical-dictionary.com (search "Animal Model"), 2005, 1 page.
Medtronic, Inc., Annual Report (Form 10-K) (Jun. 28, 2011) 44 pages.
Millard, F. C., et al, "Renal Embolization for ablation of function in renal failure and hypertension." Postgraduate Medical Journal, 65, 729-734, (1989).
Oliveira, V., et al., "Renal denervation normalizes pressure and baroreceptor reflex in high renin hypertension in conscious rats." Hypertension, 19:II-17-II-21 (1992).
Ong, K. L., et al. "Prevalence, Awareness, Treatment, and Control of Hypertension Among United States Adults 1999-2004." Hypertension, 49: 69-75 (2007) (originally published online Dec. 11, 2006).
Ormiston, John et al., "First-in-human use of the OneShot™ renal denervation system from Covidien." EuroIntervention, vol. 8, 2013, 4 pages.
Ormiston, John et al., "Renal denervation for resistant hypertension using an irrigated radiofrequency balloon: 12-month results from the Renal Hypertension Ablation System (RHAS) trial." EuroIntervention, vol. 9, 2013, 5 pages.

(56) **References Cited**

OTHER PUBLICATIONS

Pedersen, Amanda, "TCT 2012: Renal denervation device makers play show and tell." Medical Device Daily, Oct. 26, 2012, 2 pages, <http://www.medicaldevicedaily.com/servlet/com.accumedia.web.Dispatcher?next=bioWorldHeadlines_article&forceid=80880>.
Peet, M., "Hypertension and its Surgical Treatment by bilateral supradiaphragmatic splanchnicectomy" Am J Surgery (1948) pp. 48-68.
Renal Denervation (RDN), Symplicity RDN System Common Q&A (2011), 4 pages, http://www.medtronic.com/rdn/mediakit/RDN%20FAQ.pdf.
Schauerte, P., et al. "Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation." Circulation, 102:2774-2780 (2000).
Schlaich, Markus et al., "Renal Denervation in Human Hypertension: Mechanisms, Current Findings, and Future Prospects." Curr Hypertens Rep, vol. 14, 2012, 7 pages.
Schmid, Axel et al., "Does Renal Artery Supply Indicate Treatment Success of Renal Denervation." Cardiovasc Intervent Radiol, vol. 36, 2013, 5 pages.
Schmieder, Roland E. et al., "Updated ESH position paper on interventional therapy of resistant hypertension." EuroIntervention, vol. 9, 2013, 9 pages.
Sievert, Horst, "Novelty Award EuroPCR 2010." Euro PCR, 2010, 15 pages.
Solis-Herruzo et al., "Effects of lumbar sympathetic block on kidney function in cirrhotic patients with hepatorenal syndrome," J. Hepatol. 5 (1987), pp. 167-173.
Stella, A., et al., "Effects of reversible renal deneravation on haemodynamic and excretory functions on the ipsilateral and contralateral kidney in the cat." Hypertension, 4:181-188 (1986).
Stouffer, G. A. et al., Journal of Molecular and Cellular Cardiology, vol. 62, 2013, 6 pages.
Swartz, J.F., et al., "Radiofrequency endocardial catheter ablation of accessory atrioventricular pathway atrial insertion sites." Circulation, 87: 487-499 (1993).
Uchida, F., et al., "Effect of radiofrequency catheter ablation on parasympathetic denervation: A comparison of three different ablation sites." PACE, 21:2517-2521 (1998).
Verloop, W. L. et al., "Renal denervation: a new treatment option in resistant arterial hypertension." Neth Heart J., Nov. 30, 2012, 6 pages, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547427/>.
Weinstock, M., et al., "Renal denervation prevents sodium rentention and hypertension in salt sensitive rabbits with genetic baroreflex impairment." Clinical Science, 90:287-293 (1996).
Wilcox, Josiah N., Scientific Basis Behind Renal Denervation for the Control of Hypertension, ICI 2012, Dec. 5-6, 2012. 38 pages.
Worthley, Stephen et al., "Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial." European Heart Journal, vol. 34, 2013, 9 pages.
Worthley, Stephen, "The St. Jude Renal Denervation System Technology and Clinical Review." The University of Adelaide Australia, 2012, 24 pages.
Zuern, Christine S., "Impaired Cardiac Baroflex Sensitivity Predicts Response to Renal Sympathetic Denervation in Patients with Resistant Hypertension." Journal of the American College of Cardiology, 2013, doi: 10.1016/j.jacc.2013.07.046, 24 pages.
Bello-Reuss, E. et al., Effects of Acute Unilateral Renal Denervation in the Rat, J Clin Invest, 1975, 56: 10 pgs.
Gonschior, P., Comparison of Local Intravascular Drug-Delivery Catheter Systems, Am. Heart J., Dec. 1995, 130:6, 1174-81.
European Search Report for App. No. 12189194.9, Mailed Aug. 1, 2013, 11 pages.
Beale et al., "Minimally Invasive Treatment for Varicose Veins: A Review of Endovenous Laser Treatment and Radiofrequency Ablation". Lower Extremity Wounds 3(4), 2004, 10 pages.
Miller, Reed, "Finding a Future for Renal Denervation With Better Controlled Trials." Pharma & Medtech Business Intelligence, Article # 01141006003, Oct. 6, 2014, 4 pages.
Papademetriou, Vasilios, "Renal Denervation and Symplicity HTN-3: "Dubium Sapientiae Initium" (Doubt is the Beginning of Wisdom)", Circulation Research, 2014; 115: 211-214.
Papademetriou, Vasilios et al., "Renal Nerve Ablation for Resistant Hypertension: How Did We Get Here, Present Status, and Future Directions." Circulation. 2014; 129: 1440-1450.
Papademetriou, Vasilios et al., "Catheter-Based Renal Denervation for Resistant Hypertension: 12-Month Results of the EnligHTN I First-in-Human Study Using a Multielectrode Ablation System." Hypertension. 2014; 64: 565-572.
Doumas, Michael et al., "Renal Nerve Ablation for Resistant Hypertension: The Dust Has Not Yet Settled." The Journal of Clinical Hypertension. 2014; vol. 16, No. 6, 2 pages.
Messerli, Franz H. et al. "Renal Denervation for Resistant Hypertension: Dead or Alive?" Healio: Cardiology today's Intervention, May/Jun. 2014, 2 pages.

Figure 1

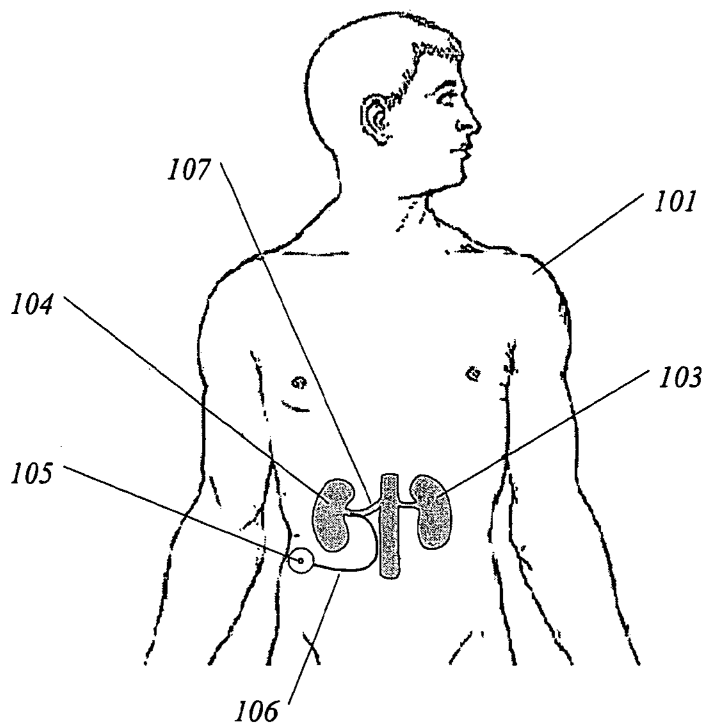
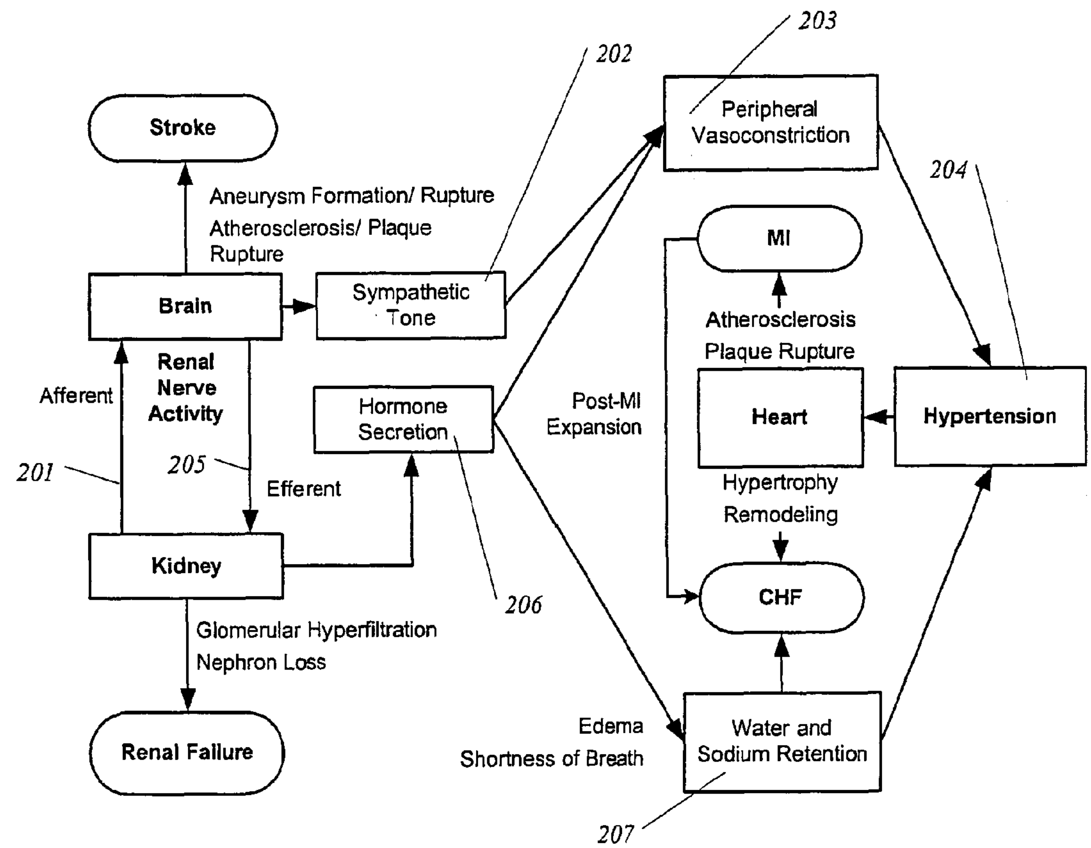


Figure 2



Stroke
Aneurysm Formation/ Rupture
Atherosclerosis/ Plaque Rupture
Brain
Sympathetic Tone
202
203
Peripheral Vasoconstriction
204
MI
Atherosclerosis
Plaque Rupture
Renal Nerve Activity
Afferent
201
205
Efferent
Hormone Secretion
Post-MI Expansion
Heart
Hypertension
Hypertrophy
Remodeling
Kidney
206
CHF
Glomerular Hyperfiltration
Nephron Loss
Renal Failure
Edema
Shortness of Breath
Water and Sodium Retention
207

Figure 3

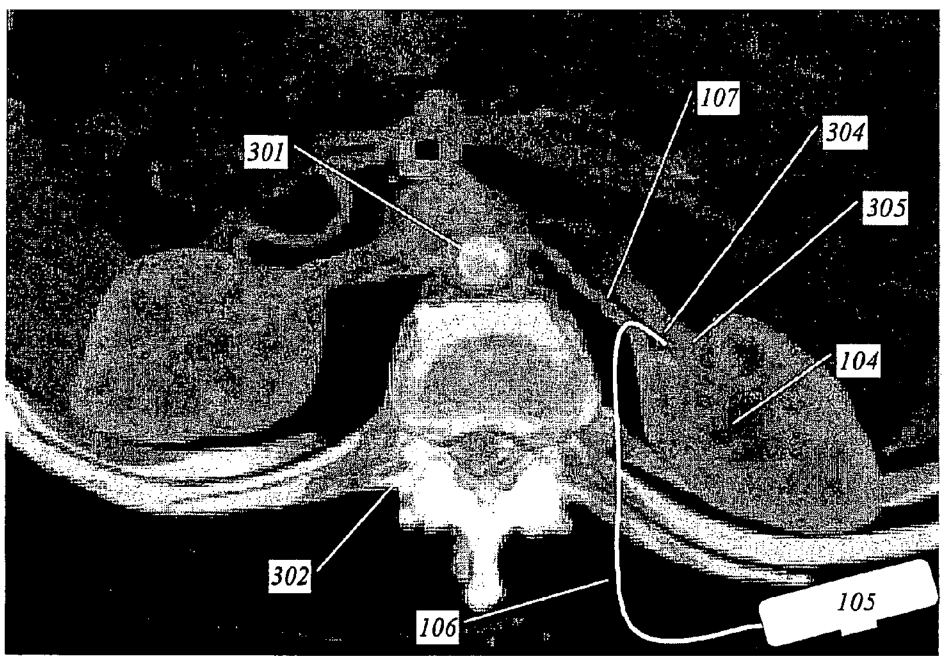
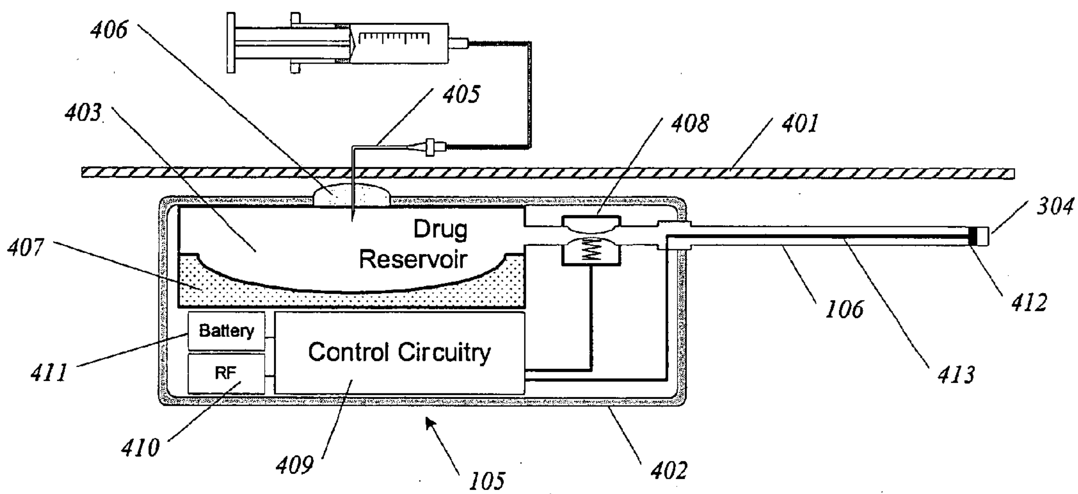


Figure 4



406
405
403
408
401
304
407
Drug
Reservoir
106
412
411
Battery
Control Circuitry
413
RF
410
409
105
402

Figure 5

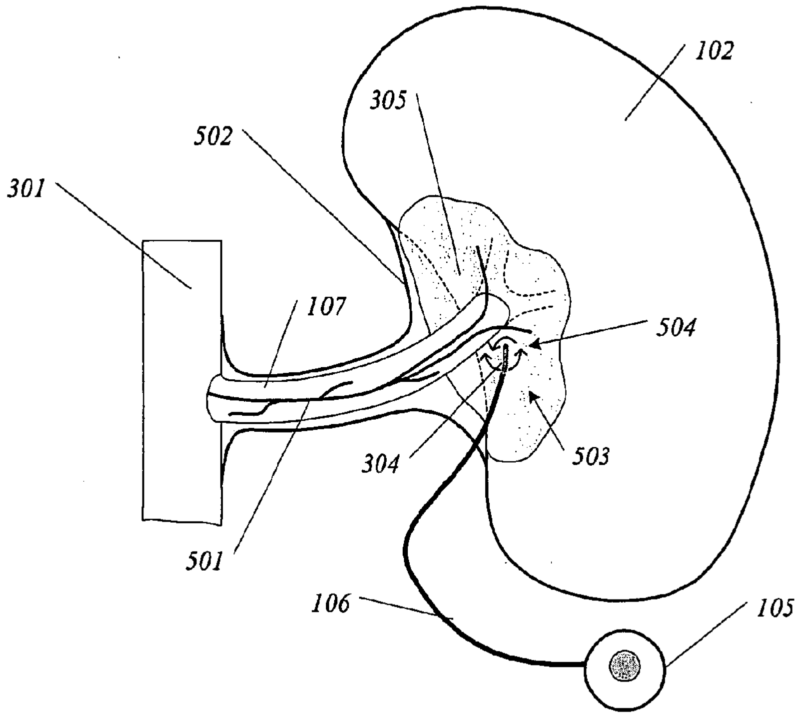


Figure 6

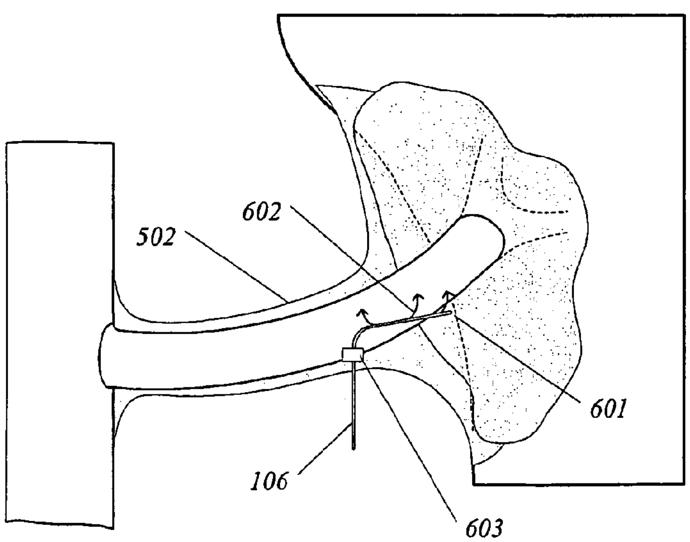


Figure 7

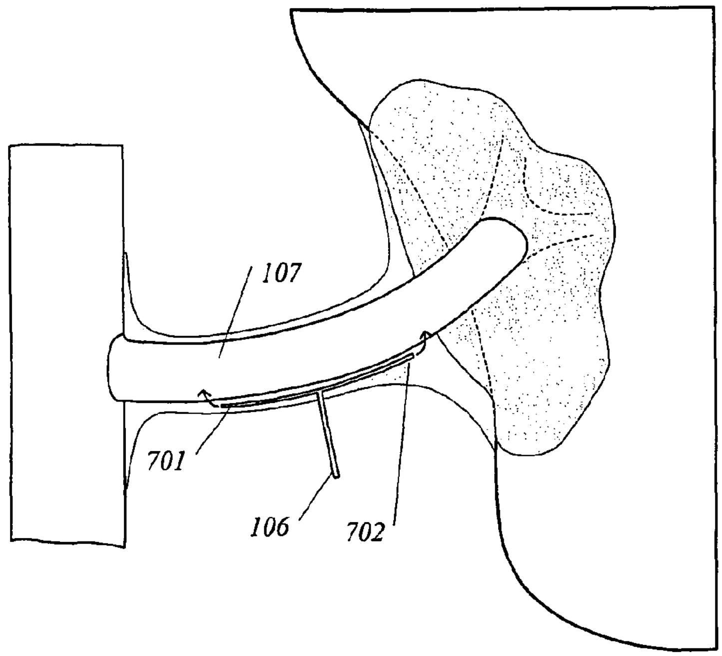


Figure 8

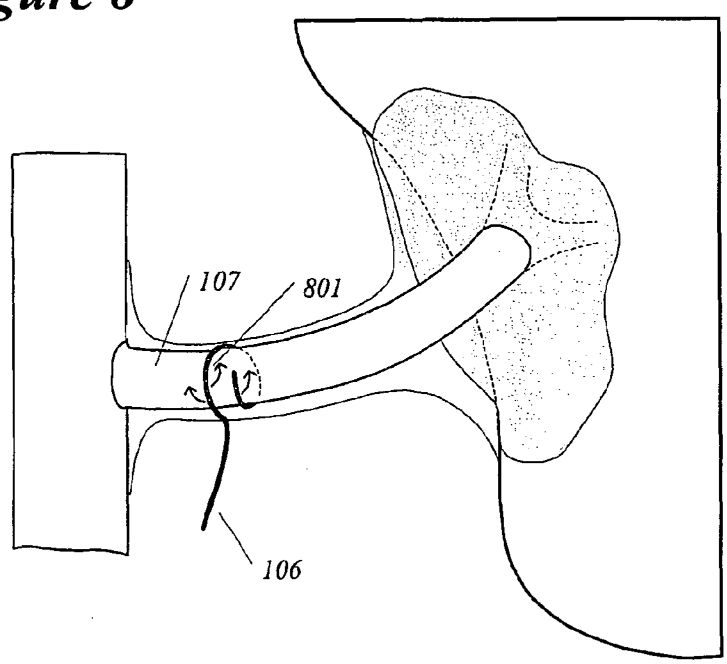


Figure 9

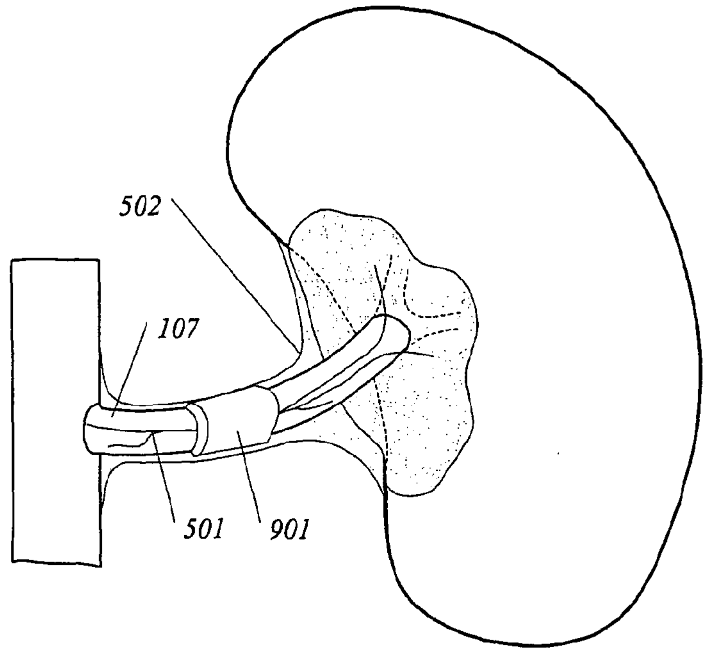


Figure 9A

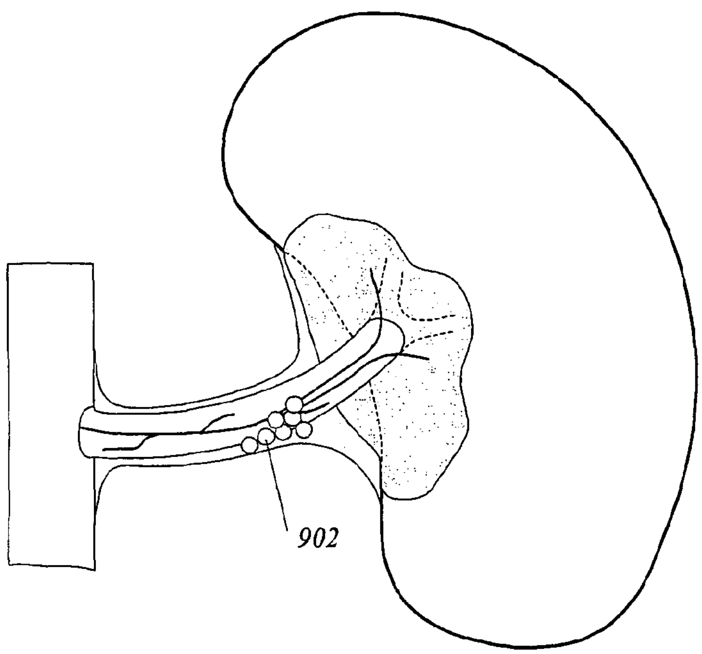


Figure 10

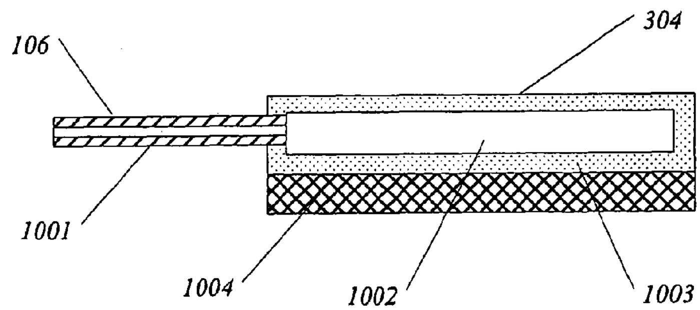


Figure 11

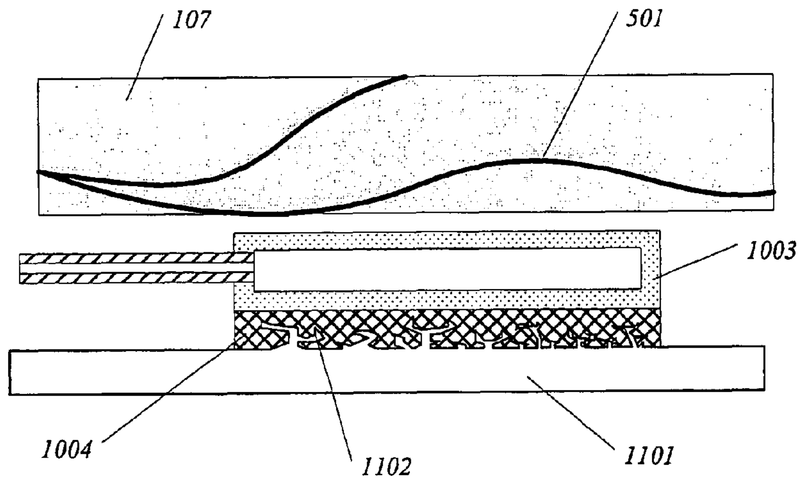


Figure 12

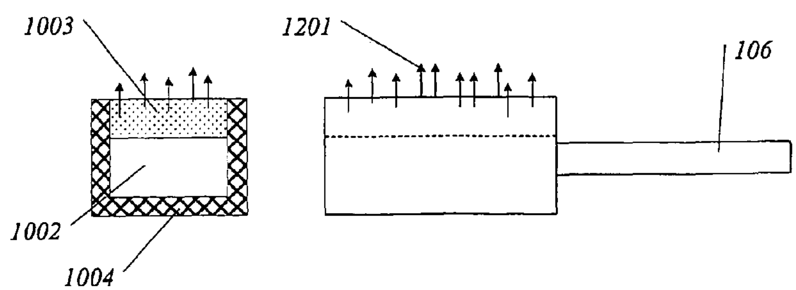
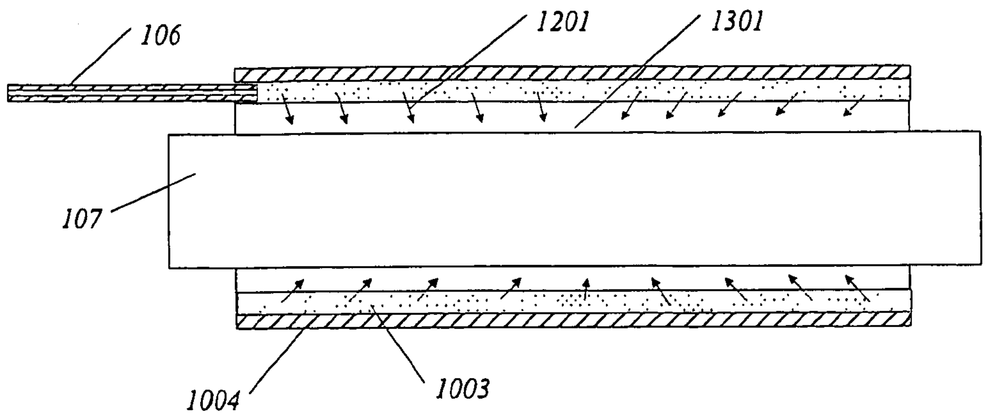


Figure 13



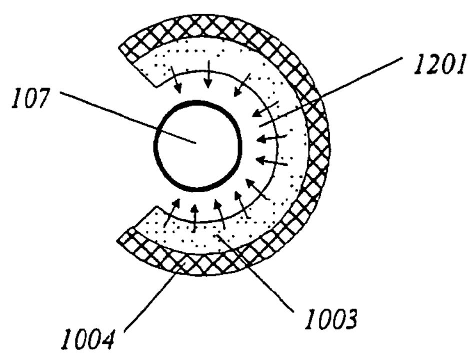


Figure 14

METHODS FOR RENAL NERVE BLOCKING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 11/133,925 filed May 20, 2005, which is a continuation of U.S. application Ser. No. 10/900,199, filed Jul. 28, 2004, now U.S. Pat. No. 6,978,174, which is a continuation-in-part of U.S. application Ser. No. 10/408,665, filed Apr. 8, 2003, now U.S. Pat. No. 7,162,303, which claims priority to the following commonly-owned applications: U.S. Provisional Application No. 60/370,190, filed Apr. 8, 2002, entitled "Modulation Of Renal Nerve To Treat CHF", U.S. Provisional Application No. 60/415,575, filed Oct. 3, 2002, entitled "Modulation Of Renal Nerve To Treat CHF", and U.S. Provisional Application No. 60/442,970, filed Jan. 29, 2003, entitled "Treatment Of Renal Failure And Hypertension". The entirety of each of these applications is incorporated by reference herein.

FIELD OF THE INVENTION

This invention relates to devices and methods for local drug delivery, and in particular is directed to an implantable system for targeted delivery of a nerve blocking agent to the periarterial space of the renal artery for the purpose of blocking the renal nerve plexus, methods for implanting same, and methods and devices for treating diseases. The invention directs the nerve-blocking agent towards the nerve, prevents dissipation of the agent in the surrounding tissue and provides fixation of the drug delivery mechanism in the surrounding tissue.

BACKGROUND OF THE INVENTION

Hypertension (HTN) and congestive heart failure (CHF) are the most important problems in contemporary cardiology. These chronic diseases account for most cardiovascular morbidity and mortality, and, despite much progress, remain therapeutic challenges. The cornerstone of therapy for both HTN and CHF includes the use primarily oral and intravenous drugs acting directly or indirectly on the kidney, such as angiotensin converting enzyme (ACE) inhibitors and diuretics, with the amount of each drug used dependent on the stage of the disease. While drug therapy is effective in the earliest stages of HTN and CHF, there is no truly effective drug treatment for the mid-to-later stages of these diseases.

HTN and CHF have many different initial causes. Irrespective of initial cause, both diseases follow a common pathway in their progression to end-stage disease, primarily as the result of excessive activity of the renal nerve. It has been shown in accepted animal models that renal denervation can control HTN and improve symptoms and slow down the progression of CHF. However, no drug or device therapies currently exist that can provide long-term, clinically usable blocking of renal nerve activity in humans. The only available clinical method of renal denervation is an invasive surgical procedure, technically difficult and of limited use, as the nerve quickly regenerates.

Of particular significance for this invention is the CHF condition that develops in many patients following a myocardial infarction (MI). Coronary artery disease causes approximately 70% of congestive heart failure. Acute MI due to obstruction of a coronary artery is a common initiating event that can lead ultimately to heart failure. This process by which this occurs is referred to as remodeling and is described in the text Heart Disease, 5th ed., E. Braunwald, Ch. 37 (1997). Remodeling after a myocardial infarction involves two distinct types of physical changes to the size, shape and thickness of the left ventricle. The first, known as infarct expansion, involves a localized thinning and stretching of the myocardium in the infarct zone. This myocardium can go through progressive phases of functional impairment, depending on the severity of the infarction. These phases reflect the underlying myocardial wall motion abnormality and include an initial dyssynchrony, followed by hypokinesis, akinesis, and finally, in cases that result in left ventricular aneurysm, dyskinesis. This dyskinesis has been described as "paradoxical" motion because the infarct zone bulges outward during systole while the rest of the left ventricle contracts inward. Consequently, end-systolic volume in dyskinetic hearts increases relative to nondyskinetic hearts.

The second physical characteristic of a remodeling left ventricle is the attempted compensation of noninfarcted region of myocardium for the infarcted region by becoming hyperkinetic and expanding acutely, causing the left ventricle to assume a more spherical shape. This helps to preserve stroke volume after an infarction. These changes increase wall stress in the myocardium of the left ventricle. It is thought that wall tension is one of the most important parameters that stimulate left ventricular remodeling. In response to increased wall tension or stress, further ventricular dilatation ensues. Thus, a vicious cycle can result, in which dilatation leads to further dilatation and greater functional impairment. On a cellular level, unfavorable adaptations occur as well. This further compounds the functional deterioration.

Takashi Nozawa et al reported the effects of renal denervation in "Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats" published in Heart Vessels (2002) 16:51-56 Springer-Verlag. In rats the bilateral renal nerves were surgically denervated (cut) (RD) two days before MI was induced by coronary artery legation. Four weeks later, left ventricular (LV) function and sodium excretion were determined. In MI rats, RD improved the reduced sodium excretion. MI RD rats revealed lower LV end-diastolic pressure and greater maximum dP/dt as compared with those of MI innervation (INN) rats. LV end-diastolic and end-systolic dimensions were significantly smaller and LV fractional shortening was greater in MI RD rats than in MI INN rats.

Inventors described novel methods and devices for reversible minimally invasive modulation of the renal nerve in copending applications. This application describes novel drug delivery methods and integrated physiological drug delivery and sensing systems that provide a significantly more effective method of blocking the renal nerve for the purpose of treating HTN and CHF than are currently available. The objective of this invention is a fully implantable device that blocks renal nerve activity of at least one kidney that 1) can be placed in a minimally invasive manner and 2) requires minimal intervention by the patient and physician; and will greatly increase patient compliance leading to a higher overall effectiveness of these therapies. In addition, to HTN and CHF, this method may be applicable to other major diseases such as slowing the progression of chronic renal failure and reducing the number of patients requiring chronic hemodialysis.

Nerve blocking in humans is known and practiced mostly in the field of local anesthesia and pain control. While compounds utilized as general anesthetics reduce pain by producing a loss of consciousness, local anesthetics act via a loss of sensation in the localized area of administration in the body. The mechanism by which local anesthetics induce their effect, while not having been determined definitively, is generally thought to be based upon the ability to locally interfere with the initiation and transmission of a nerve impulse, e.g., interfering with the initiation and/or propagation of a depolarization wave in a localized area of nerve tissue. The actions of local anesthetics are general, and any tissue where nerve conduction, e.g., cell membrane depolarization occurs can be affected by these drugs. Thus, nervous tissue mediating both sensory and motor functions can be similarly affected by local anesthetics. Neurotoxins are the chemicals that when applied to nerve tissue in extremely small amounts can block a nerve for a period of time that significantly exceeds that achieved with local anesthetics. They are also more toxic and potentially more dangerous to the patient than local anesthetics.

Different devices and formulations are known in the art for administration of local anesthetics. For example, local anesthetics can be delivered in solution or suspension by means of injection, infusion, infiltration, irrigation, topically and the like. Injection or infusion can be carried out acutely, or if prolonged local effects are desired, localized anesthetic agents can be administered continuously by means of a gravity drip or infusion pump. Thus, local anesthetics such as bupivacaine have been administered by continuous infusion, e.g., for prolonged epidural or intrathecal (spinal) administration. For prolonged control of pain fully implantable pumps have been proposed and implemented. These pumps can store a certain amount of drug and a physician periodically refills those. Several authors proposed drug eluding implants for control of pain and muscle spasms that slowly release an anesthetic agent at the site of implantation.

The duration of action of a local anesthetic is proportional to the time during which it is in actual contact with the nervous tissues. Consequently, procedures or formulations that maintain localization of the drug at the nerve greatly prolong anesthesia. Local anesthetics are potentially toxic, both locally and via systemic absorption, yet must be present long enough to allow sufficient time for the localized pain to subside. Therefore, it is of great importance that factors such as the choice of drug, concentration of drug, and rate and site of administration of drug be taken into consideration when contemplating their use for the application to block renal nerve. Charles Berde in "Mechanisms of Local Anesthetics" (Anesthesia, 5th addition, R. D. Miller, editor, Churchill-Livingstone, Philadelphia 2000, pp. 491-521) stipulated that only 1-2% of the total amount of local anesthetic, when delivered by traditional methods, ever reaches the nerve. The rest of the drug is dissipated by circulation of blood that takes the drug away, not towards the nerve. It is therefore the purpose of this invention to maximize the amount of drug directed towards the nerve so as to achieve the effective blockade of the renal nerve with the minimal amount of drug.

Theoretically, a suitable commercially available implantable drug pump such as a Syncromed pump made by Medtronic Inc. (Shoreview, Minn.) can be used to block the renal nerve in a human. The pump can deliver common commercially available solution of a local anesthetic agent such as bupivacaine to the tissue surrounding the renal nerve via an attached catheter. Although feasible, such embodiment of the renal nerve block will have practical limitations. To block a peripheral nerve (for example, for the purpose of a commonly performed brachial plexus block) using conventional techniques the physician typically infiltrates 10-50 ml of bupivacaine or similar anesthetic into the tissue surrounding the targeted nerve. This usually achieves adequate blocking of both sensory and motor signals for 2 to 6 hours. Commercially available bupivacaine marketed as Marcaine or Sensorcaine is available in concentrations of 0.25 to 0.1%. For peripheral (single nerve) blocks concentrations of 0.5 to 0.75% are typically used. There are several reasons why local anesthetics are so diluted. An amino-amide compound such as bupivacaine can be toxic both locally (it is an irritant) and systemically (it depresses the heart). It is generally perceived that a local anesthetic will not be effective below certain minimum concentration and will be toxic above certain maximum concentration.

Implantable drug pumps are commonly equipped with an internal drug storage reservoir of 30 to 50 ml. Bigger reservoirs are possible but impose severe limitations on the physical and clinical acceptability of the implant. If the continuous (24 hour a day 7 days a week) block of the patient's renal nerve is desired, and a conventional peripheral nerve blocking technique is used, the implanted pump reservoir will need to be refilled every day or even more frequently. This is possible but not practical, since refilling of the pump is associated with the skin puncture, causing pain and leading to the risk of local and systemic infection. Also, daily infusion of a large amount of drug can result in a serious risk to the patient's health, especially if the patient has a weak heart. Notably the same drug bupivacaine is effective in a much lower doze when delivered directly to the targeted nerve tissue in the patient's spine. For example, an effective intrathecal (spinal) pain block can be achieved with 2-5 ml of bupivacaine. This observation shows that more targeted delivery of the same drug to the nerve tissue can result in 10 times or more reduction of the amount of drug needed for nerve blocking.

It is therefore the purpose of this invention to provide novel methods and implantable devices that will effectively block renal nerve by targeting the delivery of the selected drug to the nerve, reducing dissipation of the drug into the surrounding tissue, reducing the amount of drug stored in the device and increasing the time interval between the refilling or replacement of the device. It is also the purpose of this invention to enable testing of the effectiveness of the renal nerve blockade and to perform the renal block automatically, intermittently and/or periodically in the clinical scenarios where the continuous block is not desired.

SUMMARY OF THE INVENTION

Surgical denervation of the kidney in experimental animals suggested multiple immediate and long-term benefits for patients with cardiac and renal diseases. The most significant potential beneficial effects are: slowing of the progression of CHF, resolution of fluid overload in CHF by induction or enhancement of diuresis, reduction of remodeling after a myocardial infarct, reduction of hypertension and slowing of the progression of chronic renal disease to dialysis. The benefits are achieved via the reduction of the systemic sympathetic tone causing vasoconstriction of blood vessels, reduction of the load on the heart and the direct effects of denervation on the kidney. Both single kidney denervation and bilateral denervation have potential benefits. Surgical denervation has been previously performed in animals and in few humans to control pain. It requires a major surgery, and is ineffective in long term, since renal nerves eventually grow back. Additionally, after the surgical denervation, the renal nerve can re-grow in a pathological way and can cause pain and other serious side effects. Since fibrotic changes at the site of denervation make repeat surgical denervation impossible, patients face the possibility of the removal of the kidney to control the pain.

The inventors suggest an alternative method of reducing or blocking the renal nerve activity in patients by minimally invasive renal nerve modulation. Renal nerve modulation is achieved by controlled infusion of a nerve-blocking agent into the periarterial space of the renal artery of the kidney. The periarterial space is the area surrounding the renal arteries and veins, extending from the aorta and vena cava to and including the area around the kidney itself. Since renal nerves follow the external surface of the renal artery, when an effective concentration of the nerve-blocking agent is present in this periarterial space, the renal nerve activity is substantially reduced or stopped. Methods and devices for both continuous and intermittent periodic blocking of the renal nerve are proposed. These methods and devices provide effective, reversible nerve blocking for a clinically relevant duration of time, while avoiding major surgery and irreparable damage to the nerve that characterize the previously used surgical denervation.

The preferred embodiment devices can be implantable drug pumps or drug eluding implants. Both classes of local drug delivery devices are known. Implanted pumps have been successfully used previously for control of pain by infusion of local anesthetics into the patient's spine. Implantable pumps range from simple reservoirs (ports) implanted under the skin with an attached catheter to sophisticated microprocessor driven programmable devices similar to pacemakers. Drug eluding implants have been used to deliver birth control agents and to prevent restenosis of coronary arteries.

Implanted pumps can also be refilled with drug without surgery using a transdermal port accessible with a needle, though it is preferable to extend the time between refillings to minimize pain and the risk of infection. The programmable implantable pump embodiment also has an advantage of the periodic drug delivery that can be adjusted up or down using a remote communication link. This is particularly significant in treatment of chronic diseases such as CHF where the continuous constant nerve blocking can result in adaptation (resting of the physiologic gain or compensation) and the loss of therapeutic effect.

Drug eluding implants work primarily by diffusion. Drug eluding implants are advantageous in the treatment of a temporary condition such as infarct expansion following acute MI where an implant that blocks the nerve for approximately 30 days and then dissolves on its own can be the best embodiment of the invention.

SUMMARY OF THE DRAWINGS

A preferred embodiment and best mode of the invention is illustrated in the attached drawings that are described as follows:

FIG. **1** illustrates the patient treated with an implanted pump embodiment of the invention.

FIG. **2** illustrates the physiologic mechanisms of renal nerve modulation.

FIG. **3** illustrates anatomic positioning of the renal nerve blocking device.

FIG. **4** illustrates an implantable drug infusion pump with a catheter electrode.

FIG. **5** illustrates the infusion of an anesthetic drug into the renal fatpad.

FIG. **6** illustrates a catheter with a cuff for distributed drug infusion into the periarterial space.

FIG. **7** illustrates a bifurcated catheter for drug infusion into the periarterial space.

FIG. **8** illustrates a coiled catheter for drug infusion into the periarterial space.

FIG. **9** illustrates a drug eluding implant in the periarterial space.

FIG. **9**A illustrates a drug eluding biodegradable material in the periarterial space.

FIG. **10** illustrates a porous drug infusion catheter.

FIG. **11** illustrates a drug infusion catheter with tissue ingrowth.

FIG. **12** illustrates the drug infusion catheter that directs the drug towards the renal nerve.

FIG. **13** illustrates the drug infusion catheter that overlaps the renal artery and directs the drug infusion towards the renal nerve.

FIG. **14** is a cross-sectional view of the catheter and artery shown in FIG. **13**.

DETAILED DESCRIPTION OF THE INVENTION

For the proposed clinical use, the capability of the invention is to block the sympathetic activity of the renal nerve of the kidney by controlled local delivery of a nerve-blocking agent with the goal of improving the patient's renal and cardiac function. Elements of the invention are useful for blocking nerves for the purpose other than treating cardiorenal disease and can be applied in other anatomic locations.

A nerve blocking agent is a drug that reduces or blocks conduction of signals by renal nerves. The nerve blocking agents used can be selected from different groups including (1) local anesthetics, (2) ketamine (a well known sedative with nerve blocking properties), (3) tricyclic antidepressants such as amitriptyline, (4) neurotoxins such as tetrodotoxin and saxitoxin or (5) any other class or type of agent that transiently or permanently, partially or completely alters nerve conduction. The terms nerve blocking agent and nerve blocking drug are interchangeable.

Cardiorenal disease is defined as a condition, chronic or acute, that involves both the heart and the kidney. Examples of cardiorenal diseases are hypertension and CHF. Cardiorenal diseases are characterized by the elevated activity of the renal nerve.

For the purpose of this invention, the renal nerve is defined as a any individual nerve or plexus of nerves and ganglia that conducts a nerve signal to and/or from the kidney and is anatomically located on the surface of the renal artery, parts of aorta where the renal artery branches from the aorta and/or on branches of the renal artery. The renal nerve generally enters the kidney in the area of the hilum of the kidney, but may enter in any location where a renal artery or branch of the renal artery enters the kidney.

Periarterial space is defined as the space immediately surrounding the renal arteries, renal veins and their branches between the aorta and the hilum of the kidney. The renal fat pad is defined as the adipose tissue or fat that fills the periarterial space and surrounds the renal artery, renal vein, renal nerves and the kidney itself. The renal fascia is the layer of connective tissue that surrounds, envelopes and contains the renal artery, renal vein, renal fatpad and the kidney itself.

An implantable or implanted device (commonly termed an "implant") is an artificial device fully enclosed in the patient's body. It is significant that implants allow the natural skin of the patient to serve as a barrier against infection. An implant can be, for example, a complex electromechanical pump, catheter and port or a drug-releasing polymer. Implantation can be achieved by open surgery, minimally invasive surgery or a transcatheter intervention, whether extravascular, intravascular or combination of any of the above. During the implantation procedure, a surgical instrument or catheter is used to cross the skin, penetrating into the patient's body. The implant is positioned at the desired site and the pathway used to access the site is closed. The site heals and the device is now fully implanted.

An implantable pump is an implantable device that is inserted under the patient's skin and can be refilled using a transdermal needle access. An implantable pump may have an integral catheter or can be equipped with a separate catheter that delivers medication to the periarterial space. Depending on the desired treatment modality, a preferred implantable pump can be programmable, patient controlled or a constant rate device.

A drug eluding implant is a device that is fully implanted in the body that slowly eludes the nerve-blocking agent into the target space. One example of such a space is the renal periarterial space. Another example is inside the renal capsule, or the virtual space between the kidney tissue and the fibrous sheath surrounding the kidney tissues itself. Drug eluding implants work by diffusion and can be biodegradable or not. An osmotic pump is also a drug eluding implant. Different matrixes that serve to slow down the diffusion of the drug into a target space are all called drug eluding implants for the purpose of this invention. These include gels, patches, injectable microspheres, suspensions, solutions or any other matrix that may hold sufficient drug to cause the intended effect.

FIG. **1** illustrates a patient **101** treated with the preferred embodiment of the invention. Patient has kidneys **103** and **104** that are bean shaped organs 12 cm long, 6 cm wide, 3 cm thick located outside and behind the peritoneal cavity. Patient is equipped with an implantable drug pump **105** implanted in the patient's side under the skin. The pump is equipped with a drug delivery catheter **106** that terminates in the area of the renal artery **107** where the delivered drug is capable of blocking the renal nerve.

FIG. **2** illustrates the role of renal nerve activity in the progression of chronic cardiac and renal diseases. Increased renal afferent (from the kidney to the brain) nerve activity **201** results in the increased systemic sympathetic tone **202** and vasoconstriction (narrowing) **203** of blood vessels. Increased resistance of blood vessels results in hypertension **204**. Hypertension is a major contributor to the progression of chronic heart failure and renal failure as well as the acute events such as strokes and myocardial infarcts. Increased renal efferent (from the brain to the kidney) nerve activity **205** results in further increased afferent renal nerve activity, secretion of the renal hormone renin **206**, and reduction of renal blood flow and the decreased water and sodium excretion by the kidney. Renin contributes to systemic vasoconstriction of blood vessels **203**. In combination these renal factors result in fluid retention **207** and increased workload of the heart thus contributing to the further deterioration of the patient. It should be clear from the FIG. **2** that moderation of renal nerve activity will benefit patients with heart, kidney and circulatory system (cardiorenal) diseases.

FIG. **3** illustrates a preferred embodiment of the invention using a CT scan (digital X-ray) image of a human body. The pump **105** is implanted under the skin in the patient's back. The pump is equipped with the catheter **106**. Tip **304** of the catheter resides near the renal artery **107**. In this example, the tip **304** is shown in the hilum **305** area of the kidney where the renal blood vessels (arteries and veins) enter and exit the kidney. In clinical practice, the tip could reside in other locations within the renal periarterial space as long as the position allows the spread of the nerve blocking agent to at least a sufficient area of the nerve to achieve the required level of nerve blockade. Each kidney has an outer convex surface and an indentation on the inner side called the hilum. The hilum functions as a route of entry and exit for the blood vessels, lymph vessels, nerves and ureters of the kidney. Renal nerves follow the renal artery **107** that connects the kidney **104** to the aorta **301** shown in front of the spine **302**. Kidney and renal vessels are enclosed in fat and fascia made of connective tissues that do not show well on this type of CT scan image.

It is significant that the catheter **106** can be introduced into the periarterial space under the CT guidance without surgery. The spatial resolution of modern imaging modalities such as CT, CT Fluoroscopy, Ultrasound and MRI allows an interventional radiologist to position the catheter within a millimeter from the renal artery of a human. The procedure is performed using a needle, an exchange guidewire and similar techniques commonly used in interventional radiology. The distal end of the catheter can be left outside of the body for the test period or the entire treatment if the treatment requires only a short duration. Later, if the renal nerve blocking therapy is clinically successful, an implanted pump or a simple subcutaneous port such as a commercially available Port-A-Cath device can be connected to the already implanted catheter for repeat infusions of the nerve-blocking drug.

FIG. **4** illustrates a simplified design of an implantable programmable drug infusion pump. The pump **105** in implanted in a pocket under the patient's skin **401**. All the mechanisms of the pump are enclosed in a titanium or polymer case **402**. Drug is stored in the reservoir **403**. To refill the pump a needle **405** is used to puncture the skin and the pump reservoir septum **406**. Septum **406** is made of a material such as silicon that seals after the puncture. Drug is displaced from the reservoir by the compressed propellant **407**. The propellant can be a chlorofluorocarbon, butane or other similar compound. The propellant acts on the drug through the elastic diaphragm **408**. Alternatively, the diaphragm can act as a spring or it can be acted upon by the spring to displace the drug. The catheter **106** is in fluid communication with the reservoir **403**. The propellant urges the drug from the reservoir into the catheter and through the catheter to the site of delivery, in this case, periarterial space of the renal artery and the renal nerve. To control the release of the drug, a valve **408** is placed between the reservoir and the catheter. The valve is normally closed. When it is forced open by the pump electronic control circuitry **409** for a short duration of time, a bolus of drug is released from the pump to the renal nerve-blocking site. The internal battery **411** supplies energy to the electronics and the valve. The communication electronics **410** allows the physician to reprogram the pump altering the amount and frequency of drug delivery as well as to interrogate the device. The communication electronics can be a radio-frequency RF link. All the elements described above are known to the developers of implantable drug pumps.

Programmable implantable infusion devices (also called implantable pumps) that actively meter the drug into an associated drug delivery catheter are described in the U.S. Pat. Nos. 4,692,147; 5,713,847; 5,711,326; 5,458,631; 4,360,019; 4,487,603; and 4,715,852. Alternatively, implantable infusion devices can control drug delivery by means of a rate-limiting element positioned between the drug reservoir and the delivery catheter as described in the U.S. Pat. No. 5,836,935, or by only releasing drug from the reservoir upon application of pressure to a subcutaneously positioned control device as described in U.S. Pat. Nos. 4,816,016 and 4,405,305. Implantable infusion devices have been used for intravenous, intraarterial, intrathecal, intraperitoneal, intraspinal and epidural drug delivery but not for periarterial drug infusion.

Known infusion pumps described above can be used to block the renal nerve for the purpose of treating cardiac diseases but they lack certain features needed in practical application. It is important for the physician to be able to determine that the nerve is in fact effectively blocked. In pain control applications of local anesthetics, the disappearance of the pain by itself is an indicator of an effective block. There is no natural indication of the renal nerve activity that can be simply measured. To address that problem, the pump **105** is equipped with a test electrode **412** on the tip **304** of the catheter **106**. The electrode can be a single ring or multiple electrodes made of a conductive metal such as gold, stainless steel or titanium. The electrode **412** is connected to the control circuitry of the pump **409** by a conductive wire **413** integrated inside the catheter body **106**. Except for the tip electrode **412** the wire is electrically insulated from the patient.

To test the effectiveness of the renal nerve block the control circuitry initiates an electric pulse to the electrode. To close the electric circuit the metal case **402** of the pump can be used as a second return electrode. Alternatively the catheter **106** can be equipped with more than one electrode. Low electric current pulse that can be in the range of 5-10 milliamps is passed through the tissue surrounding the electrode **412**. If the nerve block is effective, patient will have no sensation of tingling or minor electric shock. If the block is ineffective, the nerves in the surrounding tissue will conduct the pulse, causing pain that the patient then reports to the physician and the physician will be able to make adjustments to therapy such as, for example, increase the dose of drug delivered by the pump.

This aspect is similar to the surgical technique used by anesthesiologists to establish short term invasive nerve blocks during surgery. Before the start of the surgery, the anesthesiologist places a needle precisely on the nerve or plexus. To do this, a specially designed electrical nerve stimulator is used. The nerve stimulator delivers a very small electrical current, too small to be felt, to the nerve, which causes twitching of the particular muscles supplied by that nerve or plexus of nerves. In this example, the nerve serves as nothing more than a sophisticated "electrical wire", which is now conducting the current delivered by an electrical device to the muscles, in place of the normally conducted current originating from the brain. The patient will therefore experience small muscle twitches in the muscles supplied by that nerve similar to when your eye is twitching. This technique has never been previously applied to an implanted device. In the proposed invention, the physician will be able to perform the nerve block test in their office, without sophisticated surgical techniques and sterile environment. The external programmer device will initiate a command sequence that will be received by the electronics of the implanted pump using RF waves.

In an alternate embodiment, the catheter can have two or more sets of electrodes, at least one set proximal to and at least one set distal to the area of renal nerve blockade. Each set of electrodes is in sufficient proximity to the renal nerve so that it can either sense intrinsic nerve activity or stimulate nerve activity. It is clear that if the pump control circuitry initiates and electrical pulse to a one set of electrodes on one side of the block and does not record a corresponding and appropriately timed signal on the opposite side of the block, then the drug is effective in creating the nerve block. Conversely, if the electrical activity is sensed, more drug must be infused to create the desired block. It is also clear that this information can be used as feedback by the control circuitry to automatically adjust the timing and/or amount of drug released.

FIG. **5** illustrates the anatomic placement of the drug infusion catheter **106** in the periarterial space of the renal artery. Catheter **106** is shown schematically in connection to the implanted pump **105**. The kidney **102** is supplied with blood by the renal artery **107** from the aorta **301**. The periarterial space is defined as space immediately surrounding the renal arteries and veins along its length between the connection to the aorta and the hilum **305** of the kidney. The renal artery can branch into two or more arteries. The renal vein and its branches connecting the kidney to the vena cava of the patient share the space. These additional elements of the renal vascular system are omitted on FIG. **5** and the following figures for clarity but are presumed there.

Renal nerve **501** is shown schematically as a branching network attached to the external surface of the renal artery **107**. Anatomically, the renal nerve forms one or more plexi on the external surface of the renal artery. Fibers contributing to these plexi arise from the celiac ganglion, the lowest splanchnic nerve, the aorticorenal ganglion and aortic plexus. The plexi are distributed with branches of the renal artery to vessels of the kidney, the glomeruli and tubules. The nerves from these sources, fifteen or twenty in number, have a few ganglia developed upon them. They accompany the branches of the renal artery into the kidney; some filaments are distributed to the spermatic plexus and, on the right side, to the inferior vena cava.

A fibrous connective tissue layer, called the renal capsule, encloses each kidney. Around the renal capsule is a dense deposit of adipose tissue, the renal fat pad, which protects the kidney from mechanical shock. The kidneys and the surrounding adipose tissue are anchored to the abdominal wall by a thin layer of connective tissue, the renal fascia. The periarterial space of the renal artery is externally limited by renal fascia **502** that extends between the kidney and the aorta and contains renal vessels and nerves. Renal fascia presents a natural barrier to the dissipation of the infused drug **504** that is emitted from the tip of the catheter **106**. Fat fills the space between the fascia and the renal artery. In particular, there is a fat tissue layer **503** in the hilum of the kidney that surrounds the renal pedicle where arteries, nerves and veins enter the kidney. The catheter tip **304** is shown penetrating the renal fascia and the renal fat and the anesthetic drug is infused into the fatpad tissue. Although shown in the hilum of the kidney, the tip can be placed anywhere in the renal periarterial space as long as the position allows the spread of the nerve blocking agent to at least a sufficient area of nerve to achieve the required level of nerve blockade. In practice, there is an advantage to placing the tip at a location in continuity with the periarterial space fat. Anesthetic drugs such as amino ester and amino amide local anesthetics such as bupivacaine have high lipid solubility. The invention takes advantage of this. A single bolus of bupivacaine, after being infused into these areas, will be adsorbed by fat and retained at the location of the renal nerve. In this manner, the renal fat serves as storage of drug that will then be slowly released from the renal fat, and in this way, obtains the desired prolonged nerve blocking action.

FIG. **6** illustrates an alternative embodiment of the invention where the catheter **106** has a sealed tip **601** but is equipped with multiple side holes or pores **602** in the wall of the catheter. The pores can be as small as a micron in diameter. Pores less than 20 microns in diameter will allow penetration of the nerve-blocking drug through the wall of the catheter and into the periarterial space, renal fat pad and ultimately to the renal nerve target. At the same time, these small pores will discourage ingrowth of tissue into the side holes and increase the probability of the catheter patency after being implanted in the body for a long time. This design helps redistribute the anesthetic in the periarterial space between the wall of the renal artery and the renal fascia **502**. The catheter is equipped with a cuff **603** to encourage ingrowth of connective tissue and prevents escape of the infused drug through the puncture in the renal fascia. The cuff can be made of a natural or synthetic fiber material with pores larger than 20 microns and preferably 100 microns. For example, Dacron cuffs are commonly used in surgically implanted catheters for long term vascular access and dialysis in humans, Dacron cuffs support ingrowth of tissue, prevent dislodgment and provide a barrier to infection.

FIG. **7** illustrates an embodiment of the catheter **106** that bifurcates in the periarterial space of the kidney after it enters inside the renal fascia. The internal lumen of the catheter is split between two or more branches **701** and **702**. Catheter brunches can have end holes; side holes or wall pores for the delivery of medication to the renal nerve.

FIG. **8** illustrates an embodiment of the catheter **106** that forms a coil **801** inside the periarterial space. The coil can be equipped with side holes or pores to evenly distribute the infused drug in the periarterial space around the renal artery.

FIG. **9** illustrates an alternative preferred embodiment of the invention. The nerve blocking agent is stored in the drug eluding implant **901**. The implant **901** is contained in the periarterial space after the implantation surgery. Implant can be permanent or slowly biodegradable. Prior to implantation the implant is impregnated or "loaded" with a nerve-blocking agent that is gradually released over time into the periarterial space in the amount sufficient to block the renal nerve. An implantable drug eluding implant or pellet(s) made of a non-biodegradable polymer has the drawback of requiring both surgical implantation and removal. Use of a biocompatible, biodegradable implant overcomes deficiencies of nonbiodegradable implants. A biodegradable implant can release a drug over a long period of time with simultaneous or subsequent degradation of the polymer within the tissue into constituents, thereby avoiding any need to remove the implant. A degradable polymer can be a surface eroding polymer. A surface eroding polymer degrades only from its exterior surface, and drug release is therefore proportional to the polymer erosion rate. A suitable such polymer can be a polyanhydride. It is advantageous to have a surface eroding implant where the eroding surface faces the renal artery and the renal nerve. Other surfaces of the implant may be designed to erode at a slower rate or not erode at all that directing the drug towards the renal nerve target.

Implants for long-term drug delivery are known. For example, such implants have been used or proposed for delivering a birth control drug systemically (into circulation) or a chemotherapeutic agent to a localized breast tumor. Examples of such implantable drug delivery devices include implantable diffusion systems (see, e.g., implants such as Norplant for birth control and Zoladex for the treatment of prostate cancer) and other such systems, described of example in U.S. Pat. Nos. 5,756,115; 5,429,634; 5,843,069. Norplant is an example of a class of the drug eluding implants also called controlled release systems comprising a polymer for prolonged delivery of a therapeutic drug. Norplant is a subdermal reservoir implant comprised of a polymer can be used to release a contraceptive steroid, such as progestin, in amounts of 25-30 mg/day for up to sixty months. Norplant uses the DURIN biodegradable implant technology that is a platform for controlled delivery of drugs for periods of weeks to six months or more. DURIN can be adopted for delivery of an anesthetic into the periarterial space. The technology is based on the use of biodegradable polyester excipients, which have a proven record of safety and effectiveness in approved drug delivery and medical device products. DURIN technology is available from the DURECT Corporation of Cupertino, Calif.

Drug eluding implants generally operate by simple diffusion, e.g., the active agent diffuses through a polymeric material at a rate that is controlled by the characteristics of the active agent formulation and the polymeric material. An alternative approach involves the use of biodegradable implants, which facilitate drug delivery through degradation or erosion of the implant material that contains the drug (see, e.g., U.S. Pat. No. 5,626,862). Alternatively, the implant may be based upon an osmotically-driven device to accomplish controlled drug delivery (see, e.g., U.S. Pat. Nos. 3,987,790, 4,865,845, 5,057,318, 5,059,423, 5,112,614, 5,137,727, 5,234,692; 5,234,693; and 5,728,396). These osmotic pumps generally operate by imbibing fluid from the outside environment and releasing corresponding amounts of the therapeutic agent. Osmotic pumps suitable for the renal nerve blocking application are available from ALZA Corporation of Mountain View, Calif. under the brand name of Alzet Osmotic Pumps and the Duros implant. Duros implant is a miniature cylinder made from a titanium alloy, which protects and stabilizes the drug inside. Water enters into one end of the cylinder through a semipermeable membrane; the drug is delivered from a port at the other end of the cylinder at a controlled rate appropriate to the specific therapeutic agent. The advantage of drug eluding implants is that they can store a common anesthetic agent in concentration much higher than that used for common local anesthetic injections. Accurate delivery of small amounts of the drug via diffusion enables storage of the many months supply of the nerve-blocking agent in the implant and eliminates the need for frequent refills typical of an implanted drug pump. It is also clear that more than one drug can be released from the implant, that function in either in a complementary or inhibiting manner, to enhance or block the activity of each other.

FIG. **9**A illustrates an alternative embodiment of the local drug eluding system illustrated by FIG. **9**. In this embodiment the sustained release of the nerve-blocking agent is accomplished by infusing or implanting a self-forming biodegradable compound impregnated with the nerve-blocking agent in the periarterial space around the renal artery. The nerve-blocking agent is delivered in a biodegradable matrix such as an injectable get or microspheres. The action of the nerve-blocking drug is thus prolonged and can be enhanced by adding other medicaments, such as steroids, that suppress inflammation at the application site. This embodiment has an advantage of allowing better distribution and conformance of the drug eluding implant to the anatomic space surrounding the renal nerve. The carrier matrix loaded with the nerve blocking drug can be applied as a patch by the surgeon to the surface of the renal artery. Then the periarterial space will be closed and the fascia repaired. Alternatively the carrier matrix can be delivered through a needle attached to an infusion device. Such needle can be inserted into the periarterial space under CT guidance as illustrated by FIG. **3**. For delivery through a needle the matrix will need to be in the form of gel or injectable microspheres.

Patches and gels containing local anesthetics have been previously used for topical application to numb skin at the site of irritation or burn as well as for example during cataract eye surgery. One applicable gel is described in the U.S. Pat. No. 5,589,192 to Okabe, et al. "Gel pharmaceutical formulation for local anesthesia."

Injectable microparticles or microspheres or microcapsules loaded with drugs are also known. Injectable microspheres are made of degradable materials, such as lactic acid-glycolic acid copolymers, polycaprolactones and cholesterol among others. For example, U.S. Pat. No. 5,061,492 related to prolonged release microcapsules of a water-soluble drug in a biodegradable polymer matrix which is composed of a copolymer of glycolic acid and a lactic acid. The injectable preparation is made by preparing a water-in-oil emulsion of aqueous layer of drug and drug retaining substance and an oil layer of the polymer, thickening and then water-drying. In addition, controlled release microparticles containing glucocorticoid (steroid) agents are described, for example, by Tice et al. in U.S. Pat. No. 4,530,840. In another embodiment, the implanted microspheres are stable and do not degrade on their own. In this case, the microspheres are broken via external, directed application of an energy source, such as ultrasound, temperature or radiation. Breaking of the microspheres release the encapsulated drug and provide the desired physiologic effect, in this case, nerve blockade.

U.S. Pat. No. 5,700,485 to Berde, et al. titled "Prolonged nerve blockade by the combination of local anesthetic and glucocorticoid" describes in sufficient detail methods of manufacturing and application of biodegradable controlled release microspheres for the prolonged administration of a local anesthetic agent. The microspheres are formed of biodegradable polymers polyanhydrides, polylactic acid-glycolic acid copolymers. Local anesthetics are incorporated into the polymer. Prolonged release is obtained by incorporation of a glucocorticoid into the polymeric matrix or by co-administration of the glucocorticoid with the microspheres. Significantly U.S. Pat. No. 6,238,702 to the same authors entitled "High load formulations and methods for providing prolonged local anesthesia" described the polymer matrix that contained significantly higher concentration of local anesthetic than is normally used for injections. Since the periarterial space can anatomically accommodate an implant of substantial size nerve blocking for at least 30 days and more preferably several years is possible. U.S. Pat. No. 5,618,563 to Berde, et al. titled "Biodegradable polymer matrices for sustained delivery of local anesthetic agents" further elaborates on the biodegradable controlled release system consisting of a polymeric matrix incorporating a local anesthetic for the prolonged administration of the local anesthetic agent, and a method for the manufacture thereof.

FIG. **10** illustrates the design of the drug delivery catheter for the invention that improves fixation of the catheter and distribution of the infused drug in the periarterial space. After the implantation an implant and the surrounding tissue undergo changes. It is the purpose of this part of the invention to improve the interface of the drug delivery device to maximize the effect of the drug on the nerve while minimizing the amount.

The human body acts spontaneously to reject or encapsulate any foreign object, which has been introduced into the body or a specific bodily organ. In some cases, encapsulation will impede or halt drug infusion. In others, the delivery fluid will reflux from the tissue through a space opened between the exterior of the catheter and the tissue of the bore in which the catheter is received. Either of these results will greatly diminish the effect of direct infusion of medicaments on affected body tissue. Thus, the body's own natural defense systems thus tend to frustrate the procedure. The reaction of living tissue to an implant can take a number of different forms. For example, the initial response to the surgical trauma of implantation is usually called the acute inflammatory reaction and is characterized by an invasion of polymorphonuclear leukocytes (PMNs). The acute inflammatory reaction is followed by the chronic inflammatory reaction, which is characterized by the presence of numerous macrophages and lymphocytes, some monocytes and granulocytes. Fibroblasts also begin accumulating in the vicinity of the implant and begin producing a matrix of collagen. The fibroblasts and collagen form a connective tissue capsule around the implant and the chronic inflammatory cells to effectively isolate the implant and these cells from the rest of the body. Connective tissue consisting of a fine network of collagen with active producing fibroblasts accompanied by chronic inflammatory cells, capillaries and blood vessels is referred to collectively as granulation tissue.

Thus, when a material is implanted into a soft tissue bed of a living organism such as a human or an animal, a granulation tissue capsule is formed around the implant material consisting of inflammatory cells, immature fibroblasts and blood vessels. This tissue capsule usually increases in thickness with time and contracts around the implant, deforming the implantation site, and possibly the implant itself depending upon the rigidity of the implant.

Implant illustrated by FIG. **10** is the tip **304** of the drug delivery catheter **106** connected to the implanted drug pump explained earlier in this application. The tip **304** is in the fluid communication with the internal lumen **1001** of the catheter and is shown with an internal cavity **1002** to which the nerve-blocking drug is delivered by the pump **104** (See FIG. **4**). The tip is made out of the porous material, preferably a porous plastic such as for example PTFE. It is known that, when the implant is porous with pore entry diameters larger than approximately 20 microns, tissue grows into these pores. This phenomenon appears desirable to many medical device application because it makes an implant one with the implanted organ and in theory it allows tissue ingrowth into the implant and reduces capsular contraction. For example, U.S. Pat. No. 4,011,861 to Enger discloses an implantable electric terminal which has pores preferably in the range of about 10 to 500 microns so that blood vessels and tissue can grow into the pores.

The embodiment illustrated by FIG. **10** combines a material with small pores, preferably less than 20 microns **304** designed to discourage the tissue ingrowth and a material with larger pores, preferably larger than 20 microns **1004** to encourage tissue ingrowth. Material **1003** allows free diffusion and convection of the drug from the cavity **1002** to the periarterial space. Material **1004** encourages the natural fixation of the catheter tip **304** so that it will not be dislodged by motion and migrate out of the periarterial space.

FIG. **11** illustrates the catheter tip made of porous materials. It shows the surrounding tissue **1101** ingrowth **1102** into the large pore implant **1004** section. The small pore section **1003** is oriented to direct the drug infusion towards the renal artery **107** and the renal nerve **501**.

FIG. **12** further illustrates an embodiment of the porous tip of the catheter **106** for directional drug delivery. The portion of the implant that surrounds the drug filled cavity **1002** and that is oriented away from the renal nerve is made of the material **1004** that is impermeable to drug. Portion of the implant that is oriented towards the renal nerve (on the surface of the renal artery) **1003** is made of the material that is permeable to the nerve blocking agent. Drug flux **1201** is shown as unidirectional therefore directing the therapy towards the site and minimizing the loss of the drug.

FIGS. **13** and **14** further illustrate an embodiment of the porous tip of the catheter **106** that at least partially encloses or envelopes the renal artery **107** with the intention of further directing the drug delivery towards the renal nerve. The tip forms a multi-layer cuff around the artery. The outer shell **1004** of the cuff is made of the material that is impermeable to the infused drug to prevent dissipation of the said drug away from the renal nerve. The material **1004** can also have large pores to encourage ingrowth and fixation of the implant. The inner layer **1003** is made of material permeable to the nerve-blocking drug. It is in fluid communication with the delivery catheter **106**. The layer **1003** can be equipped with internal channels to facilitate equal distribution of drug **1201** in the space **1301** between the cuff and the artery **107**.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

What is claimed is:

1. A method for treatment of a human patient diagnosed with hypertension, the method comprising:
   positioning a catheter in a periarterial space of a renal artery and proximate a renal nerve of the patient; and
   delivering a nerve blocking agent via the catheter to inhibit neural traffic along the renal nerve,
   wherein delivering the nerve blocking agent results in a therapeutically beneficial reduction in blood pressure of the patient.

2. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery and proximate a renal nerve comprises positioning the catheter near a renal hilum of the patient.

3. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery and proximate a renal nerve comprises positioning the catheter within a renal hilum of the patient.

4. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery and proximate a renal nerve comprises positioning a distal tip of the catheter within a target site in continuity with a periarterial fat tissue layer surrounding a renal pedicle of the patient.

5. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery and proximate a renal nerve comprises positioning a distal tip of the catheter within renal fascia of the patient.

6. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery comprises intravascularly delivering the catheter through an abdominal aorta to the renal artery of the patient.

7. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery comprises extravascularly positioning the catheter within the periarterial space.

8. The method of claim **1** wherein positioning a catheter in a periarterial space of a renal artery and proximate a renal nerve of the patient comprises delivering the catheter over a guidewire.

9. The method of claim **1** wherein the renal nerve innervates a kidney of the patient, and wherein inhibiting neural traffic along the renal nerve comprises denervating the kidney.

10. The method of claim **1** wherein inhibiting neural traffic along the renal nerve comprises ablating the renal nerve.

11. The method of claim **1** wherein delivering a nerve blocking agent via the catheter comprises delivering at least one of an anesthetic, a neurotoxin, an alcohol, and an antidepressant to the renal nerve.

12. The method of claim **1** wherein delivering a nerve blocking agent via the catheter comprises delivering an alcohol to the renal nerve.

13. The method of claim **1** wherein the catheter has a sealed tip and at least one side hole or pore through a sidewall of the catheter, and wherein delivering a nerve blocking agent via the catheter comprises delivering alcohol via the at least one side hole or pore.

14. The method of claim **1**, further comprising removing the catheter from the patient after delivering nerve blocking agent to conclude the procedure.

15. The method of claim **1** wherein inhibiting neural traffic along the renal nerve further results in a reduction of systemic sympathetic tone in the patient.

16. A method for catheter-based renal denervation of a hypertensive human patient, the method comprising:
   positioning a catheter having a drug delivery element within a renal hilum of the patient and adjacent neural fibers innervating a kidney of the patient; and
   at least partially ablating the neural fibers via a nerve blocking agent delivered from the drug delivery element,
   wherein at least partially ablating the neural fibers results in a therapeutically beneficial reduction in blood pressure in the patient.

17. The method of claim **16** wherein positioning a catheter having a drug delivery element within a renal hilum of the patient comprises positioning the catheter within a distal portion of the renal vasculature of the patient.

18. The method of claim **16** wherein the nerve blocking agent comprises at least one of an anesthetic, a neurotoxin, an alcohol, and an antidepressant.

19. The method of claim **16** wherein the nerve blocking agent comprises an alcohol.

20. The method of claim **16**, further comprising monitoring a parameter of the catheter and/or tissue within the patient before and during delivery of the nerve blocking agent from the drug delivery element.

21. The method of claim **20**, further comprising altering delivery of the nerve blocking agent in response to the monitored parameter.

22. The method of claim **16**, further comprising removing the catheter from the patient after delivering the nerve blocking agent to conclude the procedure.

23. The method of claim **16** wherein the catheter has a sealed tip and at least one aperture through a sidewall of the catheter, and wherein at least partially ablating the neural fibers via a nerve blocking agent comprises delivering alcohol via the at least one aperture.

* * * * *